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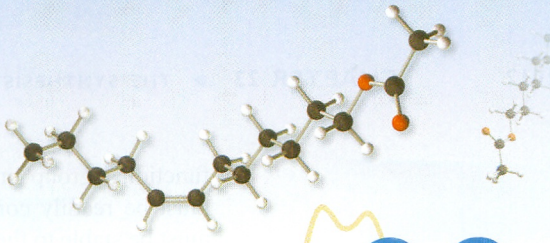

The Synthesis of Organic Compounds

CHAPTER 23

EACH OF THE PRECEDING chapters that presented new reactions contained a number of problems that required using these reactions to synthesize organic compounds. You have probably become at least somewhat comfortable in working this type of problem, even though they are among the more difficult ones in this text. In this chapter the multitude of reactions that have been presented in the previous chapters are applied to the synthesis of more complex compounds. The syntheses here are longer and require somewhat more thought than those done previously, although the general approach and strategies remain the same as those you have already learned.

In the synthesis of complex compounds, which contain more than one functional group, it is often necessary to protect one reactive functional group so that the desired reaction will occur only at the unprotected functional group. Groups that can be used to protect alcohols, aldehydes and ketones, carboxylic acids, and amines during the course of a synthesis are presented first in this chapter. Then the strategy of synthesis is discussed in somewhat more detail. This is followed by the presentation of several syntheses. Tables at the end of this chapter summarize all of the reactions that have been presented in the previous chapters and are of significant synthetic utility. Table 23.2 lists important carbon–carbon bond-forming reactions. Table 23.3 lists all of the reactions, including the carbon–carbon bond-forming reactions of Table 23.2, arranged according to the functional group that is produced in the reaction. Thus, it is possible by consulting Table 23.3 to quickly identify the various reactions that can be used to prepare a particular functional group. Note that this table also constitutes a review of most of the reactions presented in earlier chapters.

23.1 PROTECTING GROUPS FOR ALCOHOLS

As discussed in Section 18.9, a protecting group is used to protect one functional group in a complex compound from reacting while a reaction is occurring at another

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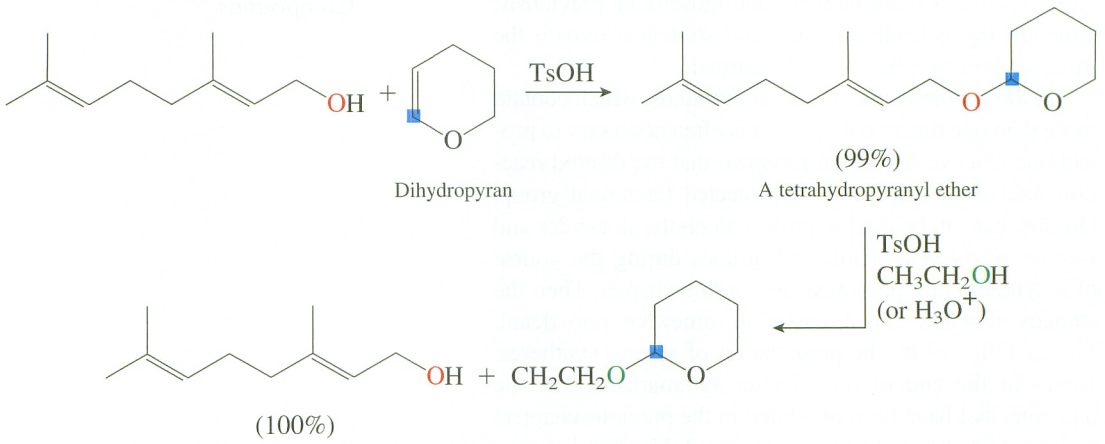
functional group in the molecule. For this process to be useful, the functional group must be readily converted to the protecting group. In addition, the protecting group must be stable to the conditions of the desired reaction. Finally, the protected functional group must be easily converted back (deprotected) to the original functional group after the desired reaction has been accomplished.

In the case of a compound containing an alcohol functional group, it is often the acidic hydrogen of the hydroxy group that causes problems when a reaction is attempted at another functional group in the compound. This hydrogen can be replaced by an alkyl group to form an ether, a rather unreactive functional group that is stable to treatment with strongly basic or nucleophilic reagents. However, simple alkyl ethers are quite difficult to cleave, so it is difficult to regenerate the alcohol from a simple alkyl ether. Therefore, if an ether is to be used as a protecting group for an alcohol, it must be specially designed for easy removal after the reaction is complete.

One method that has found widespread use for the protection of an alcohol is reaction with dihydropyran to form a tetrahydropyranyl ether. Once the desired reaction has been accomplished, the protecting group can be removed by treatment with aqueous acid or acid and ethanol. The formation of a tetrahydropyranyl ether and its cleavage are illustrated in the following equation:



The mechanism of the formation of the tetrahydropyranyl ether (see Figure 23.1) is an acid-catalyzed addition of the alcohol to the double bond of the dihydropyran and is quite similar to the acid-catalyzed hydration of an alkene described in Section 11.3. Dihydropyran is especially reactive toward such an addition because the oxygen helps stabilize the carbocation that is initially produced in the reaction. The tetrahydropyranyl ether is inert toward bases and nucleophiles and serves to protect the alcohol from reagents with these properties. Although normal ethers are difficult to cleave, a tetrahydropyranyl ether is actually an acetal, and as such, it is readily cleaved under acidic conditions. (The mechanism for this cleavage is the reverse of that for acetal formation, shown in Figure 18.5 on page 776.)

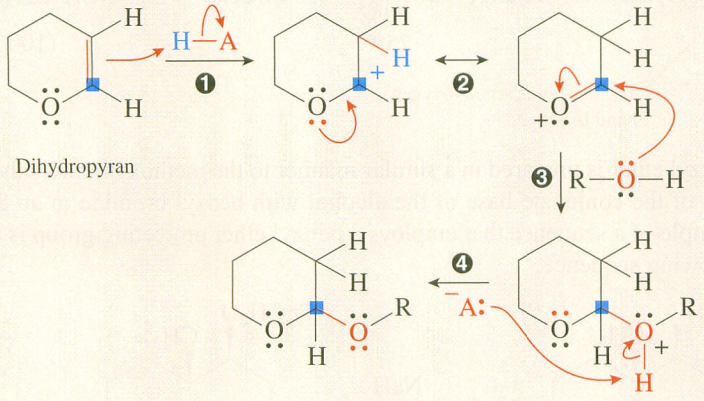
In designing a synthesis, it is useful to have available several protecting groups that are formed under, are stable to, or are cleaved by different conditions so that one can be found that is compatible with the requirements imposed by the particular functional groups and reaction conditions of the proposed synthesis. Another protecting group that is used for alcohols is the methoxymethyl ether. The protecting group is added by reacting the conjugate base of the alcohol with chloromethyl methyl ether in an S_N2 reaction. Like the tetrahydropyranyl ether, this ether is also an acetal and can be readily removed

Overall, this mechanism is similar to that for the hydration of an alkene (described in Section 11.3).

❶ A proton adds to the double bond of dihydropyran.

❷ Dihydropyran is very reactive toward addition because the carbocation that is produced is stabilized by resonance involving the electron pair on the adjacent oxygen.

❸ The oxygen of the alcohol acts as a nucleophile and bonds to the electrophilic carbon of the carbocation.

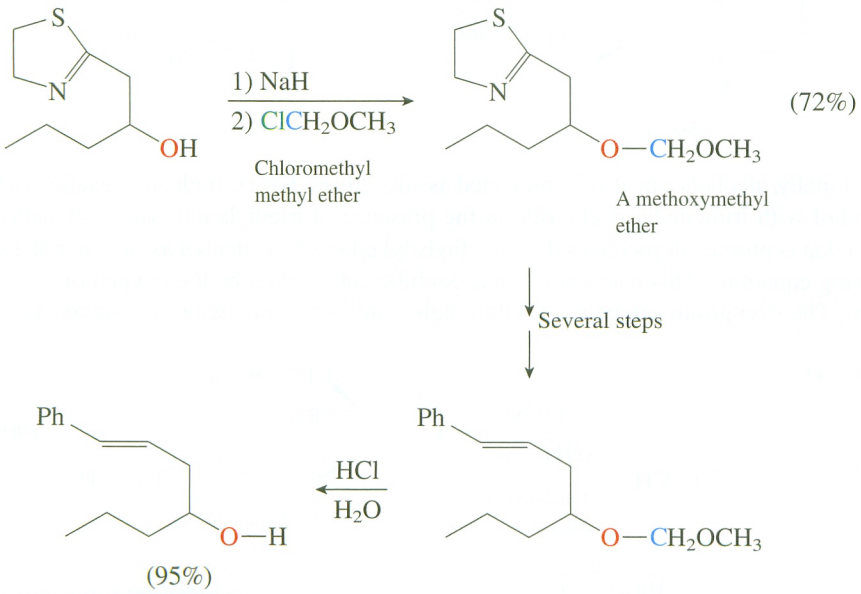


❹ Transfer of a proton to the conjugate base of the acid regenerates the catalyst and produces the tetrahydropyranyl ether.

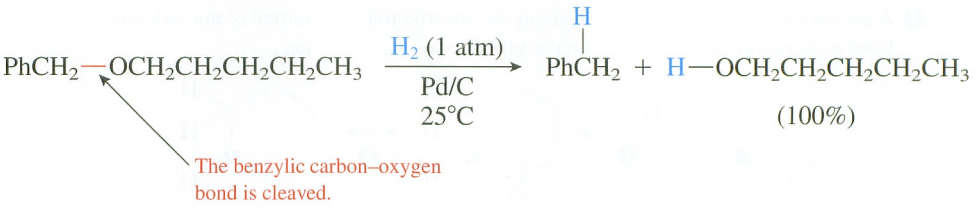
Figure 23.1

MECHANISM OF THE FORMATION OF A TETRAHYDROPYRANYL ETHER.

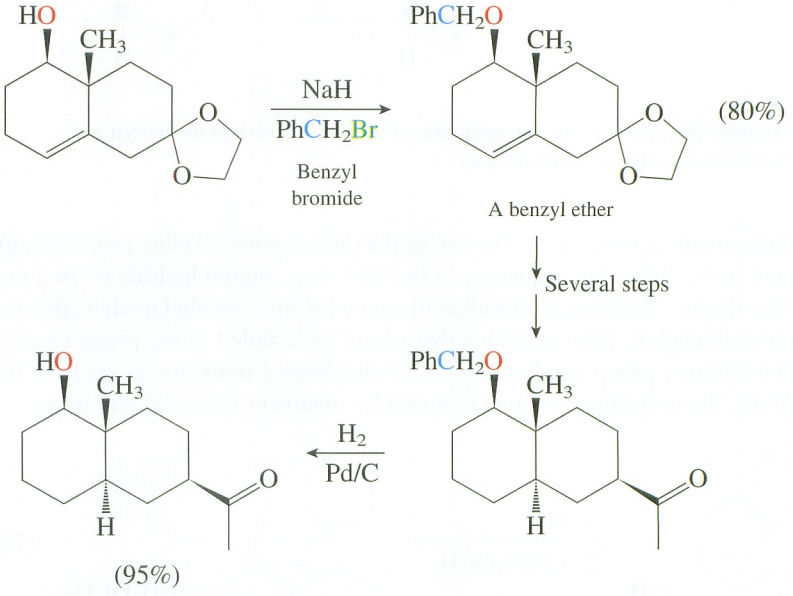
by treatment with aqueous acid. The use of the methoxymethyl ether protecting group is illustrated in the following sequence. In the first step, sodium hydride is used to deprotonate the alcohol. Reaction of this alkoxide ion with chloromethyl methyl ether provides the protected alcohol. Now reactions that would have failed in the presence of the unprotected hydroxy group can be done. After the desired transformations have been accomplished, the protecting group is removed by treatment with acid and water.



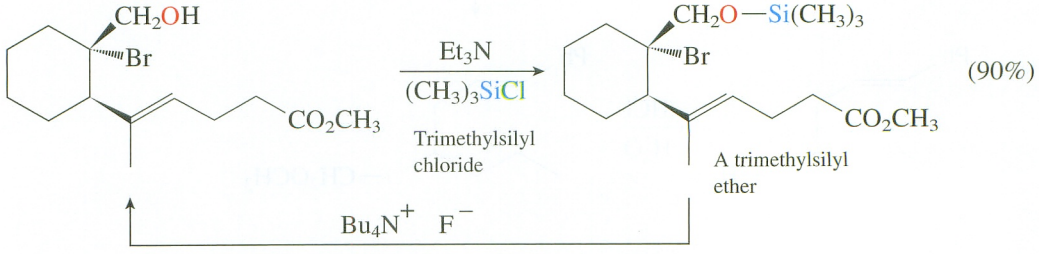
Alcohols can also be protected by conversion to a benzyl ether. The ether is stable to base and dilute acid but can be cleaved by treatment with hydrogen and a catalyst. Although most single bonds do not react with hydrogen and a catalyst, benzylic carbon–oxygen single bonds are readily cleaved under these conditions in a process called **hydrogenolysis.** An example is provided by the following equation:



The benzyl ether is prepared in a similar manner to the methoxymethyl ether, that is, by reaction of the conjugate base of the alcohol with benzyl bromide in an S_N2 reaction. An example of a sequence that employs a benzyl ether protecting group is illustrated in the following sequence:

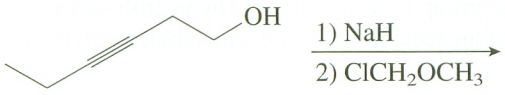


Finally, alcohols can also be protected as silyl ethers. For example, the reaction of the alcohol with trimethylsilyl chloride in the presence of triethylamine (to react with the HCl that is produced) produces the trimethylsilyl ether of the alcohol as shown in the following equation. (This reaction is a nucleophilic substitution by the oxygen on the silicon.) The silyl group can be removed in high yield by reaction with fluoride anion.



PROBLEM 23.1

Show the products of these reactions:

a) 

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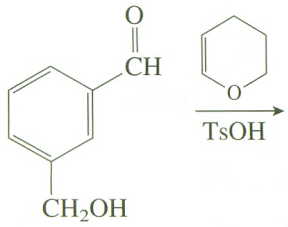
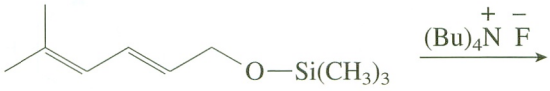
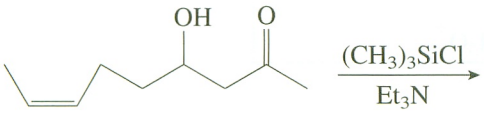
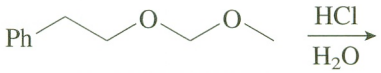
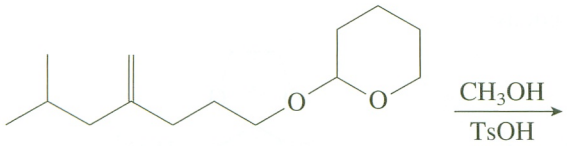
c) 

d) 

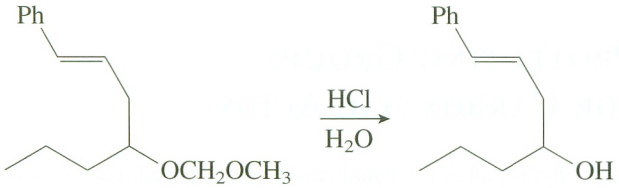
e) 

f) 

g) 

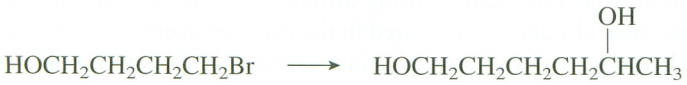
PROBLEM 23.2

Show all of the steps in the mechanism for the hydrolysis of this methoxymethyl ether. What other products are formed in this reaction?



PROBLEM 23.3

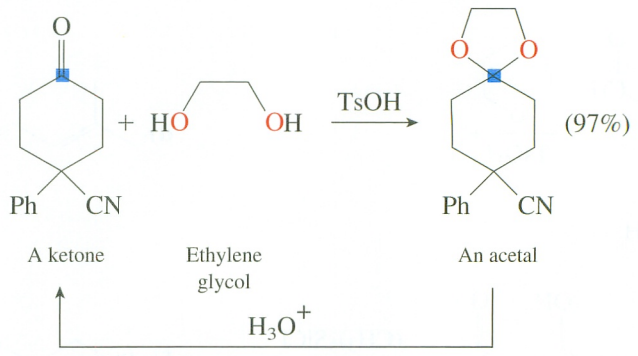
A Grignard reagent cannot be prepared from 4-bromo-1-butanol due to the presence of the acidic hydrogen of the hydroxy group. Show how the use of a protecting group enables this compound to be used to prepare 1,5-hexanediol by a Grignard reaction.



23.2 PROTECTING GROUPS FOR ALDEHYDES AND KETONES

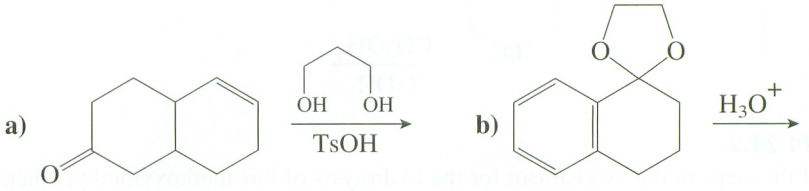
Aldehydes and ketones are usually protected by converting them to acetals by reaction with an alcohol in the presence of acid (see Section 18.9). Although many different alcohols could be used, ethylene glycol (1,2-ethanediol) or 1,3-propanediol is most often

employed because the intramolecular nature of the addition of the second alcohol group makes the equilibrium more favorable. The acetal, once formed, is stable to basic and nucleophilic reagents. The protecting group is easily removed by hydrolysis in aqueous acid. An example of the formation of an acetal by reaction with ethylene glycol is provided by the following equation:



PROBLEM 23.4

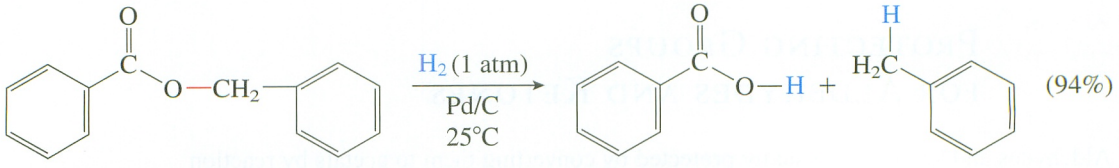
Show the products of these reactions:



23.3 Protecting Groups for Carboxylic Acids

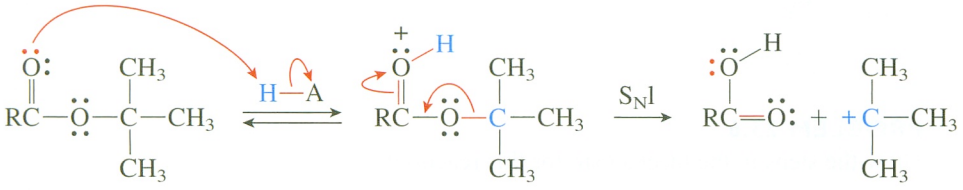
Because the acidic hydrogen is the usual cause of undesired reactivity, carboxylic acids are commonly protected as esters. Most often, simple methyl esters are used. The ester can be prepared via the acyl chloride or by Fischer esterification (see Section 19.4). The ester group can be converted back to the carboxylic acid by hydrolysis under acidic or basic (saponification) conditions (see Section 19.5).

Other esters are sometimes used to protect carboxylic acids, especially when there is a desire to deprotect the acid by using different conditions from those available for methyl esters. Benzyl esters are prepared in the usual manner but can be cleaved by reaction with hydrogen and a catalyst. Again it is the benzylic carbon–oxygen bond that is broken in the hydrogenolysis reaction:



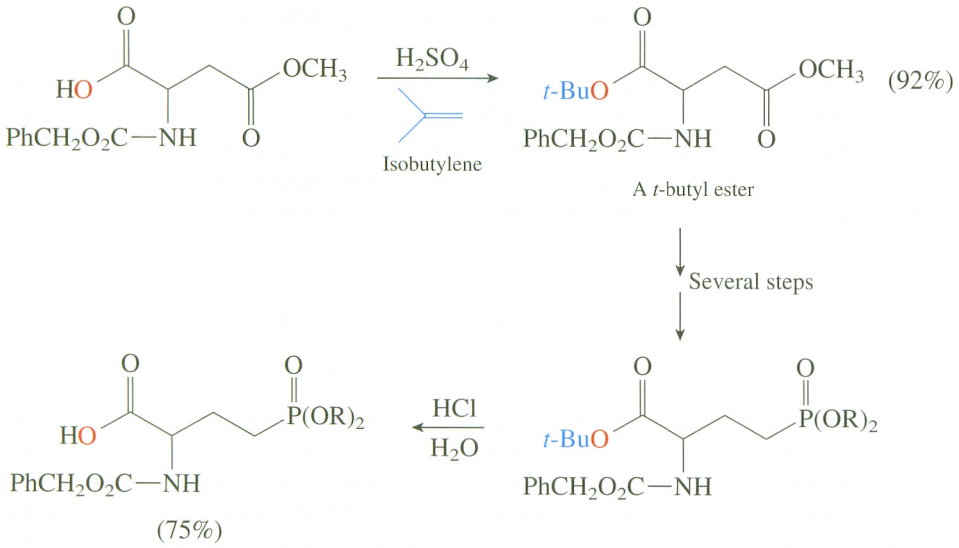
A benzyl ester

t-Butyl esters can be cleaved by reaction with dilute acid under milder conditions than those required to hydrolyze a methyl ester. The reaction follows an S_N1 mechanism, rather than the reverse of the Fischer esterification mechanism, because of the stability of the *t*-butyl carbocation:



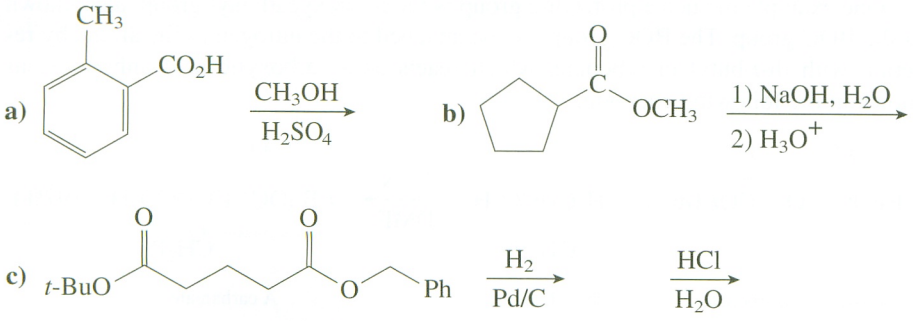
A *t*-butyl ester

The *t*-butyl ester is often prepared by acid-catalyzed addition of the carboxylic acid to isobutylene. The overall protection–deprotection sequence is outlined in the following equation. Note that the *t*-butyl group is removed in the last step without destroying the phosphorus ester or the amide or benzyl ester groups.



PROBLEM 23.5

Show the products of these reactions:



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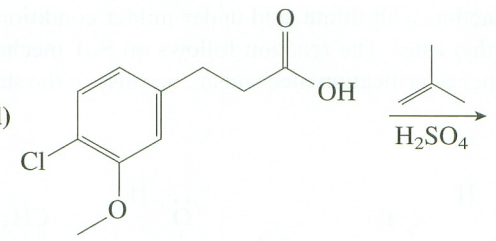
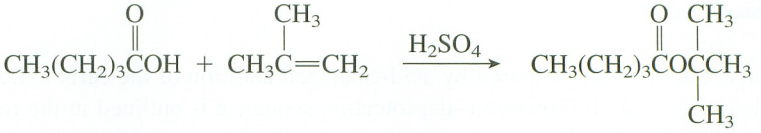


PROBLEM 23.6

Show the steps in the mechanism for this reaction:

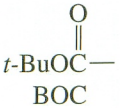


23.4 PROTECTING GROUPS FOR AMINES

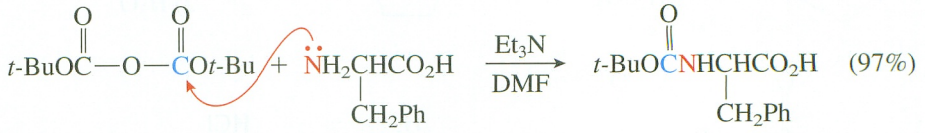
Often it is the basic and nucleophilic unshared pair of electrons on the nitrogen of an amine that causes the problem in a synthesis and needs to be protected. This electron pair can be made much less reactive by converting the amine to an amide. The electron pair on the nitrogen in the amide is delocalized by resonance onto the oxygen of the carbonyl group and is not as available to react as either a base or a nucleophile.

One example of this strategy has already been presented in Section 17.4, where conversion to an acetamide (R′ = CH_3) was used to decrease the activating ability of an amino group on a benzene ring in electrophilic aromatic substitution reactions.

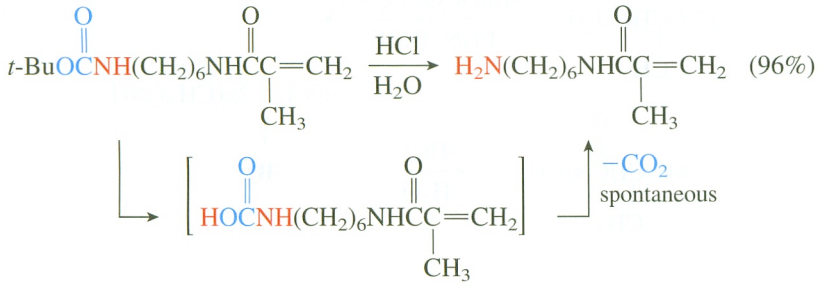
An amide is one of the more stable carboxylic acid derivatives, and rather vigorous conditions are required to hydrolyze it to regenerate the unprotected amine. Therefore, several special protecting groups that can more readily be removed have been developed. These groups still employ an amide to deactivate the nitrogen, but they all contain some feature that allows them to be removed under milder conditions. They are especially useful in the synthesis of peptides from amino acids, described in Chapter 26.



One example of such a protecting group is the *t*-butoxycarbonyl group, also known as the BOC group. The BOC group can be attached to the nitrogen of the amine by reaction with di-*t*-butyl dicarbonate, which reacts as a carboxylic acid anhydride, as shown in the following equation:

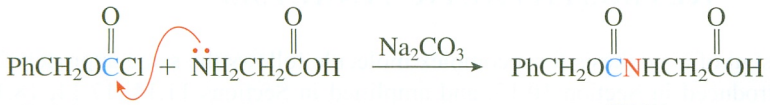


The product contains the **carbamate** functional group, which has characteristics of both an amide and an ester. Thus, the amine is protected as an "amide," but the ester part of the carbamate can be readily removed. In fact, the *t*-butyl group of the carbamate can be removed by treatment with dilute acid. (This is the same S_N1 process that is described in Section 23.3) The resulting carbamic acid is unstable and spontaneously eliminates carbon dioxide, regenerating the amine. An example is provided by the following equation:



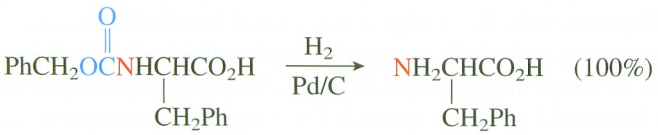
A carbamic acid

Another protecting group often employed for amines is the **benzyloxycarbonyl** group. The chemistry here is reminiscent of that of the BOC group in that the amine is protected by conversion to a carbamate. This time an acyl chloride derivative, carbobenzoxy chloride, rather than an acid anhydride derivative, is reacted with the amine.



Carbobenzoxy chloride — Glycine

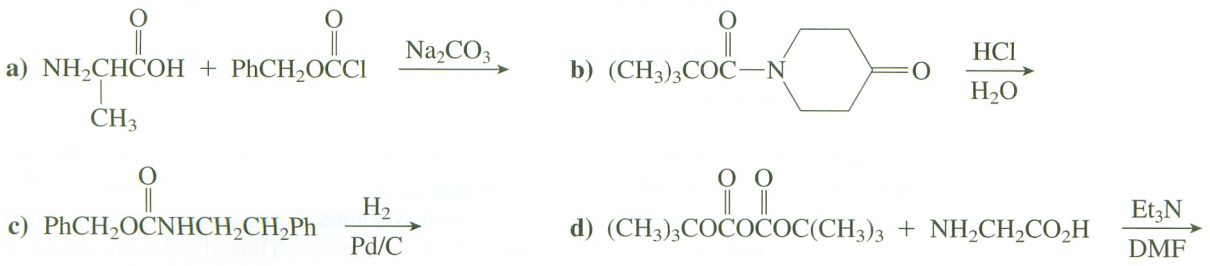
When it is time to remove the benzyloxycarbonyl protective group, the compound is reacted with hydrogen in the presence of a catalyst. The cleavage of the benzyl group by hydrogenolysis (see Section 23.3) is followed by spontaneous decarboxylation of the carbamic acid. An example is provided by the following equation:



PROBLEM 23.7

BioLink

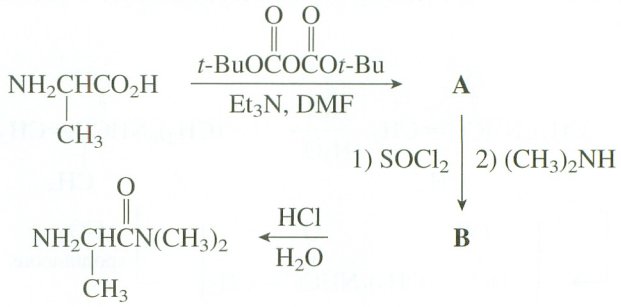
Show the products of these reactions:



BioLink

PROBLEM 23.8

An example of the use of a protecting group for an amine is provided by the following reaction scheme. Show the structures of the missing compounds, **A** and **B,** in this sequence of reactions and explain why the final amide cannot be prepared directly, that is, by reaction of the original amino acid with $SOCl_2$ followed by $(CH_3)_2NH$.



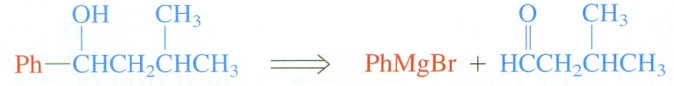
PROBLEM 23.9

Explain why the hydrolysis of **B** in problem 23.8 is selective in that the amide bond of the final product is not cleaved.

23.5 RETROSYNTHETIC ANALYSIS

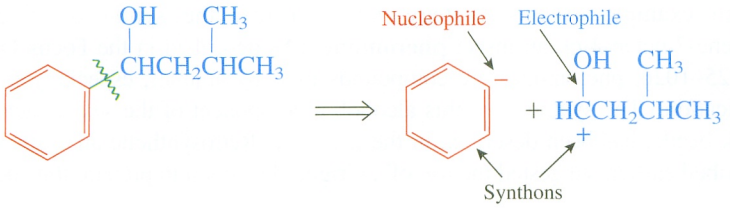
The design of a synthesis for a complex molecule follows the same approach that was first introduced in Section 10.15, and amplified in Sections 11.14, 17.14, 18.11, and 20.11, that is, working backward from the target compound or retrosynthetic analysis. Recall that this process involves envisioning a reaction that can be used to prepare the target compound from a simpler compound. This simpler compound then becomes the target for the next step, and this process is continued until a commercially available compound is reached.

When looking for reactions that can be used to prepare the target compound, we envision **bond disconnections,** or breaking bonds, at or near the functional groups in the compound. Disconnections involving carbon–carbon bonds are especially important. It is usually advantageous to have in mind a reaction that will accomplish the reverse process when the bond disconnection is made. Suppose, for example, that the target compound is 3-methyl-1-phenyl-1-butanol. The Grignard reaction provides an excellent method for the preparation of many alcohols. With this reaction in mind, a disconnection between the phenyl group and the alkyl group, as shown in the following equation, provides fragments that can be reassembled by a Grignard reaction.

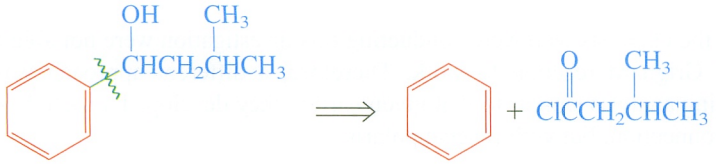


3-Methyl-1-phenyl-1-butanol

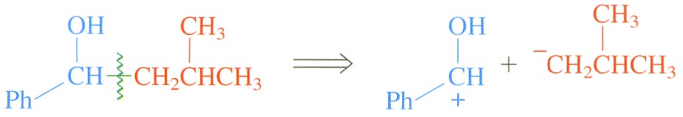
In performing a retrosynthetic analysis, it may also be useful to disconnect a bond, showing the fragments not as real compounds but only as an electrophile and a nucleophile. (The electrophile and nucleophile fragments are called **synthons.**) This may help bring to mind other reactions that can be used to reassemble the fragments. Thus, the disconnection of 3-methyl-1-phenyl-1-butanol can be written as shown in the following equation:

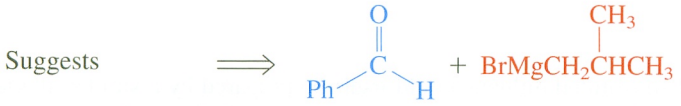


In addition to suggesting the Grignard route shown, this disconnection might bring to mind the fact that aromatic rings also react as nucleophiles in electrophilic aromatic substitution reactions. This suggests that a Friedel-Crafts acylation might be used in this synthesis. (Although the Friedel-Crafts acylation reaction produces a ketone, we recognize that an alcohol or ketone in the target is usually equivalent because either can be converted to the other by oxidation or reduction reactions.)

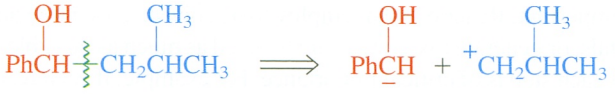


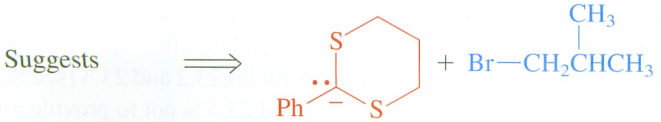
When a bond is disconnected, two polarities of the fragments are possible. Either fragment can potentially be the nucleophile, while the other is the electrophile. Let's consider the disconnection of the other carbon–carbon bond involving the hydroxy-bearing carbon of 3-methyl-1-phenyl-1-butanol. The disconnection shown in the following equation suggests another Grignard pathway:



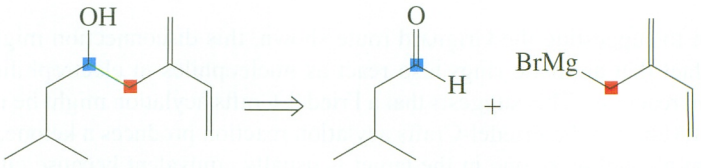


The disconnection with opposite polarity requires a very different approach—the use of a synthon that is nucleophilic at the hydroxy carbon. The acyl anion equivalent described in Section 20.9 provides a nucleophilic carbon with a substituent that can be readily converted to a hydroxy group:



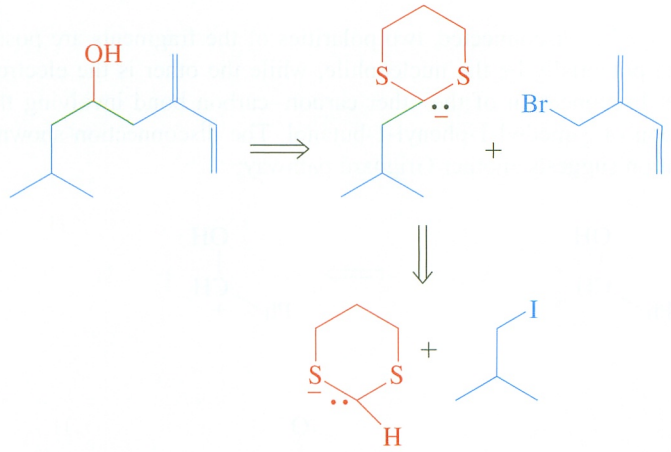


As an example of this strategy, let's consider the synthesis of 2-methyl-6-methylene-7-octen-4-ol, an insect **pheromone.** (As described in the Focus On box on pages 1025–1026, pheromones are compounds used by animals, especially insects, for communication.) The synthesis of this alcohol, a component of the sex attractant of the male bark beetle, has been described in the literature. Retrosynthetic analysis, similar to that described earlier, suggested the use of a Grignard reaction to prepare this alcohol:



2-Methyl-6-methylene-7-octen-4-ol

However, the chemists who were conducting this investigation were not able to get this particular Grignard reaction to work. Therefore, a different approach was needed. Again, using analysis similar to that given earlier, they developed a route based on the same disconnection, but with reverse polarity:



The needed substituted dithiane could itself be prepared by a similar alkylation of the unsubstituted dithiane anion. The synthesis is shown in Figure 23.2.

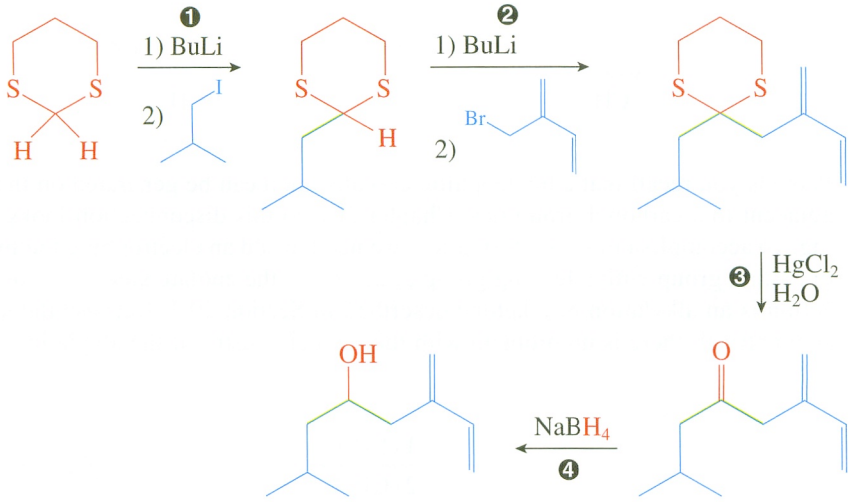
What makes a good synthesis? The answer to this question depends on many factors. The time required to complete the synthesis and the overall cost of the synthesis are factors whose relative importance often depends on whether the synthesis is being done in an academic research laboratory, an industrial research laboratory, or a factory. How much material is needed—milligrams, grams, kilograms, or tons? Today, environmental concerns are extremely important. Reactions that employ toxic solvents, use large amounts of poisonous heavy metals, or generate toxic waste are avoided as much as possible. In a long synthesis the yield of each step is of critical importance. For example, if each reaction proceeds in 90% yield, a synthesis of 10 steps has an overall yield of only 35% ($0.9^{10} = 0.35$). If each of the steps proceeds in 80% yield, the overall yield falls to 11%.

In designing a synthesis, it is important to have a wide range of reactions available to use. The reactions of most importance in synthesis that have been presented in earlier chapters in this book are summarized in Tables 23.2 and 23.3 (see Sections 23.7 and 23.8). Note that the purpose of Tables 23.2 and 23.3 is not to provide a list of reactions

❶ Butyllithium was used as a strong base to remove one of the weakly acidic hydrogens on the carbon between the sulfurs. The resulting anion was then used as a nucleophile, replacing the iodine in an S_N2 reaction (see Section 20.9).

❷ This process was repeated with a different alkyl halide. The yield in this step was 51%.

❸ The dithioacetal group was removed by hydrolysis with mercuric ion and water in 59% yield.



2-Methyl-6-methylene-7-octen-4-ol

❹ To complete the synthesis, the ketone was reduced to an alcohol. This was accomplished in 66% yield using sodium borohydride.

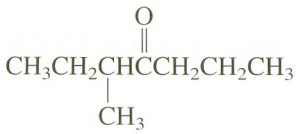
Figure 23.2

THE SYNTHESIS OF 2-METHYL-6-METHYLENE-7-OCTEN-4-OL.

for you to memorize. Rather, use these tables as references when you are designing syntheses. Table 23.2 lists important reactions that form carbon–carbon bonds. Such reactions are often the key to designing a synthesis. Table 23.3 lists all of the reactions, including those of Table 23.2, according to which functional group is formed in the product. Thus, if the target molecule is an alcohol, Table 23.3 can be consulted for a number of different methods that might be employed to prepare that alcohol.

PRACTICE PROBLEM 23.1

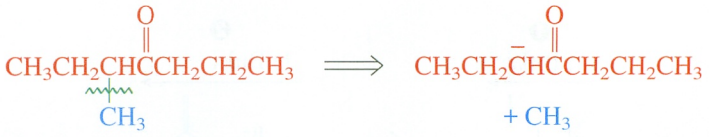
Use disconnections of carbon–carbon bonds to generate electrophile and nucleophile synthon fragments that could be used to prepare 3-methyl-4-heptanone. Then show an actual reaction suggested by these synthons.



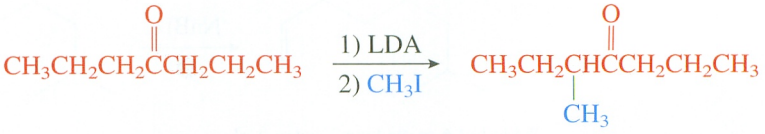
3-Methyl-4-heptanone

Solution

Because most reactions occur at a functional group or at the adjacent carbon, this is where most disconnections should be made. This usually still allows a variety of disconnections. As one possibility, let's consider disconnecting the methyl group from the α-carbon of this compound. One of the possible polarities of the synthon fragments is shown:



Perhaps you recall that a nucleophilic enolate anion can be generated on the carbon adjacent to a carbonyl group (see Chapter 20), so this disconnection looks promising. To accomplish this transformation, we need to add an electrophilic methyl group (a methyl group with a leaving group attached) to the enolate anion. The overall reaction is an alkylation of a ketone described in Section 20.3. Because the ketone is symmetrical, there is no problem with the regiochemistry of the alkylation.

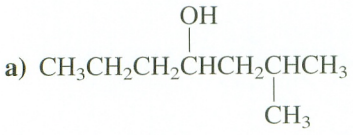


Note that numerous other disconnections might also prove useful. For example, the bond between the carbonyl carbon and one of the α-carbons can be disconnected with this polarity:

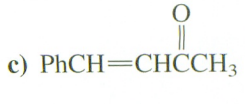
This suggests one of the ketone syntheses described in Section 19.10. How many other routes can you think of?

PROBLEM 23.10

Use disconnections of carbon–carbon bonds to generate electrophile and nucleophile synthon fragments that could be used to prepare the following compounds. Then show an actual reaction suggested by these synthons that would provide a method for the synthesis of each compound. You may find it useful to consult Table 23.2 at the end of this chapter.

a) 

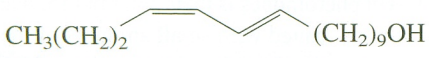
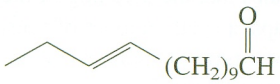
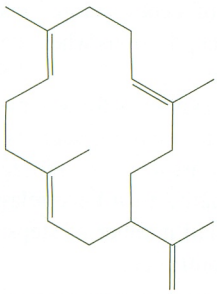
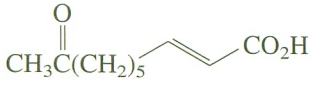
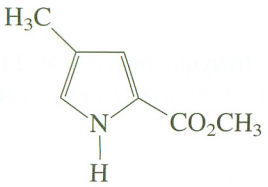
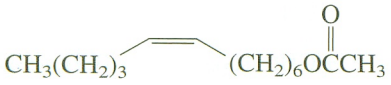
b)

c) 

Focus On Biological Chemistry

Pheromones

Insects communicate with chemicals. These chemicals are called pheromones, derived from the Greek words *pherin,* to transfer, and *hormone,* to excite. Perhaps you have seen a line of ants, all following the same invisible trail across a floor or a concrete walkway. One ant has found a food source and has laid down a chemical, a trail pheromone, on its return to the nest. Other ants then follow this chemical trail back to the food source. Insects also use pheromones extensively to attract members of the opposite sex for mating. Pheromones must be volatile enough to readily enter the gas phase so that they can be detected by the insect's antennae. This requires them to be relatively small organic compounds. Some examples of pheromones are provided in the accompanying table.

Pheromones	Source
	Bombykol or (10*E*,12*Z*)-hexadecadien-1-ol, sex attractant of the female silkworm moth
	Fumilure or 11-tetradecenal, sex attractant of the female spruce budworm; fumilure is a 96:4 ratio of *E*:*Z* geometrical isomers
	Neocembrene A, a termite trail pheromone
	Queen substance or (*E*)-9-oxo-2-decenoic acid, excreted by the queen bee to prevent the development of other queens
	Methyl 4-methylpyrrole-2-carboxylate, trail pheromone of the leaf-cutting ant
	(*Z*)-7-Dodecen-1-yl acetate, component of the sex attractant of the female elephant and numerous insects

Because of their small size, insects are able to excrete only minute amounts of a pheromone. However, these compounds are active in extremely small amounts. An insect's antennae can detect one molecule per receptor, and it has been estimated that only

Continued

100 to 1000 molecules are necessary to elicit the appropriate response. Of course, the presence of such a small amount of the pheromone in the insect makes the task of isolating enough of the compound to determine its structure quite difficult. For example, the last two abdominal segments from 78,000 female gypsy moths were needed to isolate enough of the sex pheromone dispalure to allow its structure to be determined.

The structural requirements for a pheromone to be active in a particular species are very strict. Not only must the structure be correct, but the stereochemistry of the pheromone is often of critical importance. For example, the sex attractant of the female silkworm moth is (10*E*,12*Z*)-hexadecadien-1-ol, also known as bombykol. This particular stereoisomer is 10^{12} times more active than the (10*Z*,12*Z*) or (10*E*,12*E*) stereoisomers, which differ only in the configuration about one of the double bonds. Often, a mixture of stereoisomers in a very specific ratio is necessary for maximum activity of the pheromone.

Pheromones are also important in mammals, although many fewer have been identified. As one example, (*Z*)-7-dodecen-1-yl acetate has recently been identified in the urine of female elephants when they are in heat. This ester elicits a specific sexual response in male elephants. Interestingly, this same ester is part of the pheromone mixture that many insects, especially moths, use as a sexual attractant.

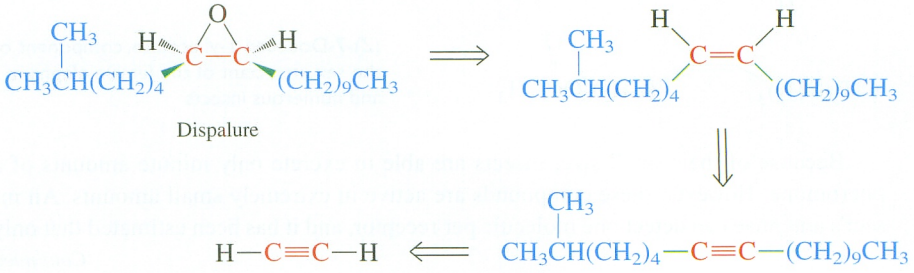
Nigel Cattlin/Holt Studios International/Photo Researchers, Inc.

One of the major reasons for the interest in insect pheromones is their potential for use to control pests. In one method a large number of traps, baited with small amounts of the sex attractant of the female insect, are used to trap enough males that the breeding of the insects is decreased. In another method that requires fewer traps, a small number of traps are used to monitor the population of the target insect. The best time to apply pesticides can be determined by monitoring these traps. In one case, 10 to 15 applications of a pesticide to control the pink bollworm still resulted in damage to 30% of a cotton crop. This was decreased to almost no damage with only one to two pesticide applications when the ideal times for these applications were determined by the use of traps.

Insect pheromones provide ideal targets for industrial organic synthesis for a number of reasons. First, pheromones cannot be isolated in quantity from natural sources, so they must be synthesized if they are to be used. In addition, they are active in minute quantities, so the synthesis of large amounts is not necessary. Finally, most have relatively simple structures and can be synthesized in a relatively small number of steps. Of course, the stereochemistry of these steps must be carefully controlled.

23.6 Examples of Syntheses

This section presents several syntheses to further illustrate retrosynthetic analysis. First, let's consider the synthesis of dispalure, the sex pheromone of the gypsy moth, a serious despoiler of forests.

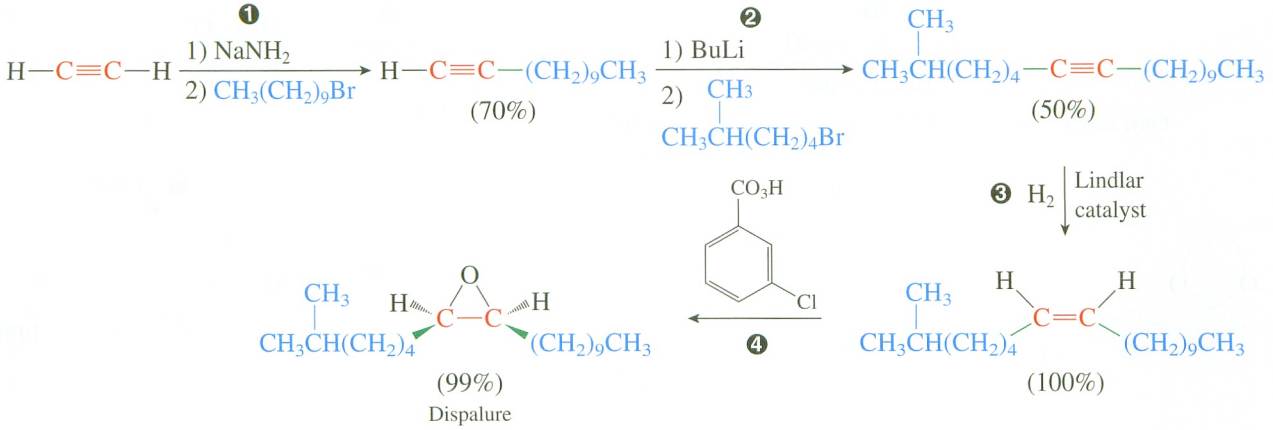


Dispalure

❶ Sodium amide, a strong base, was used to remove the acidic hydrogen of ethyne. The resulting acetylide ion was used as a nucleophile in an S_N2 substitution (see Section 10.8).

❷ This process was repeated to add the other alkyl group to the other side of the alkyne.

❸ Hydrogenation using the Lindlar catalyst resulted in the formation of the *cis*-alkene (see Section 11.12).



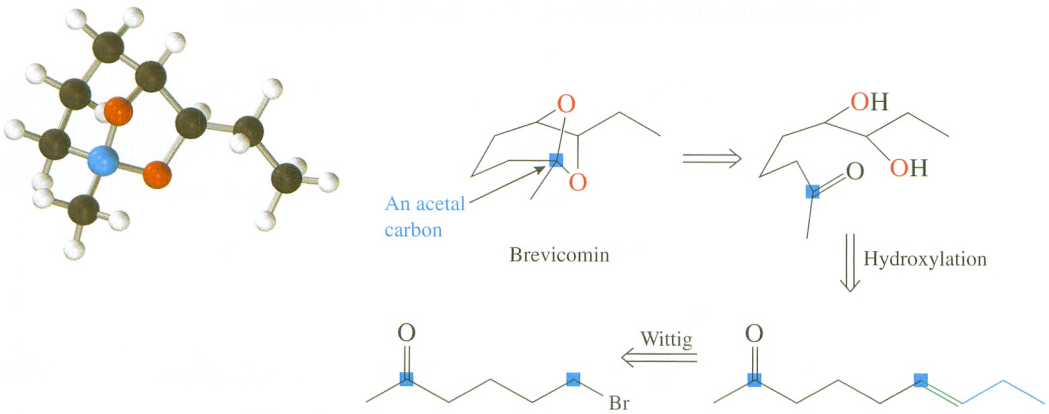
❹ The synthesis was completed by epoxidation of the alkene with *m*-chloroperbenzoic acid. This resulted in the formation of the epoxide by a syn addition (see Section 11.9).

Figure 23.3

THE SYNTHESIS OF DISPALURE.

Using retrosynthetic analysis, we recognize that the *cis*-epoxide can be prepared from the *cis*-alkene. The *cis*-alkene can be prepared by catalytic hydrogenation of an alkyne. Finally, substituted alkynes can be prepared by nucleophilic substitution reactions using acetylide ion nucleophiles (see Section 10.8). On the basis of this analysis, the synthesis reported in the literature was accomplished as shown in Figure 23.3.

As another example, let's consider the synthesis of brevicomin, the aggregation pheromone of the Western pine beetle. First, it is necessary to recognize that brevicomin is an acetal and can be disconnected into a diol and a ketone. The diol can be prepared by hydroxylation of an alkene, and the alkene can be prepared by a Wittig reaction:

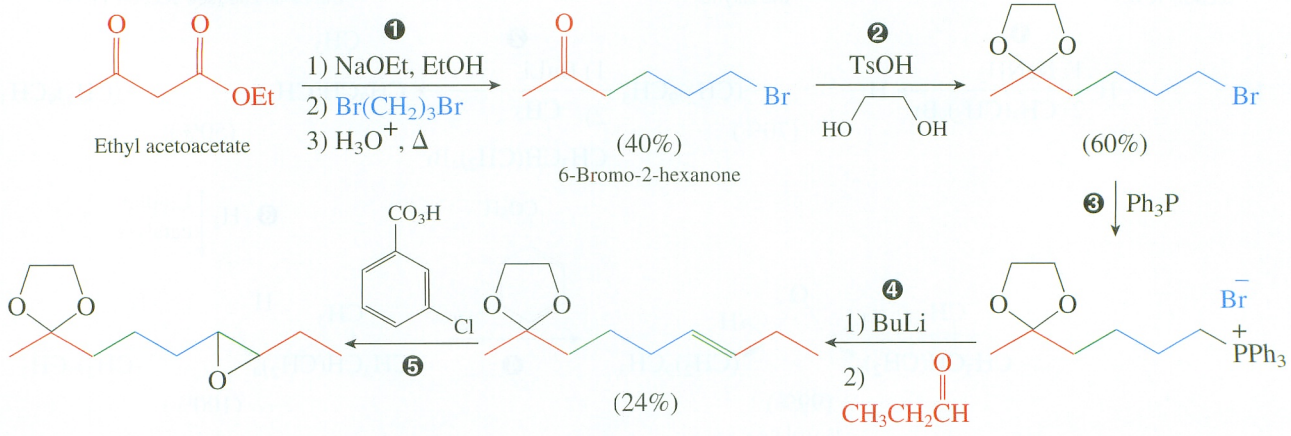


The reported synthesis was accomplished as shown in Figure 23.4.

❶ 6-Bromo-2-hexanone was prepared by an acetoacetic ester synthesis (see Section 20.4).

❷ A Wittig reaction was to be used to form the double bond of the alkene, but first the ketone had to be protected as the acetal (see Section 23.2).

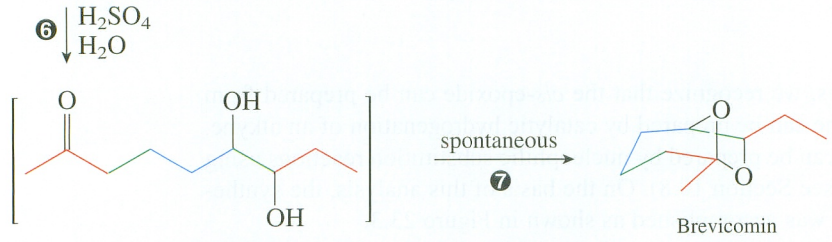
❸ The requisite phosphonium salt for the Wittig reaction was prepared by an S_N2 reaction using triphenylphosphine, a good nucleophile (see Section 10.9).



❹ A Wittig reaction (see Section 18.7) produced the alkene in 24% yield from the bromoacetal.

❺ To add the hydroxy groups, the alkene was converted to the epoxide (see Section 11.9).

❻ The hydrolysis of the epoxide to the diol was accomplished with acid and water (see Section 10.10). This step also removed the acetal protective group.

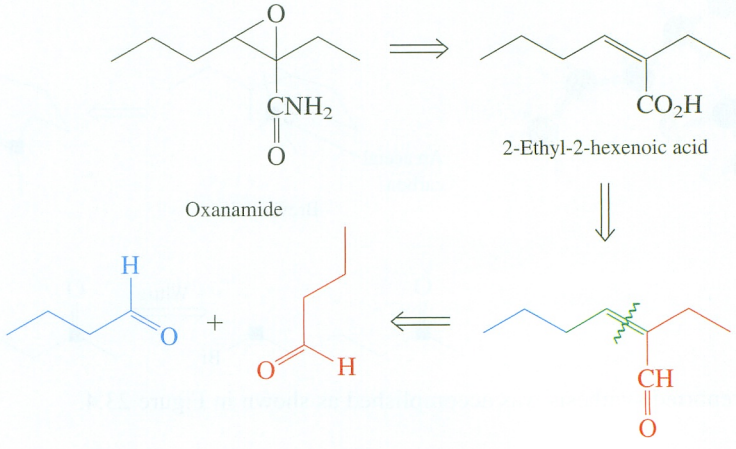


❼ The cyclization of the dihydroxy ketone to the acetal is very favorable because it is intramolecular and occurred spontaneously under the reaction conditions of the hydrolysis. Brevicomin was produced in 91% yield from the epoxide.

Figure 23.4

THE SYNTHESIS OF BREVICOMIN.

Next, let's consider the synthesis of oxanamide, a tranquilizer:



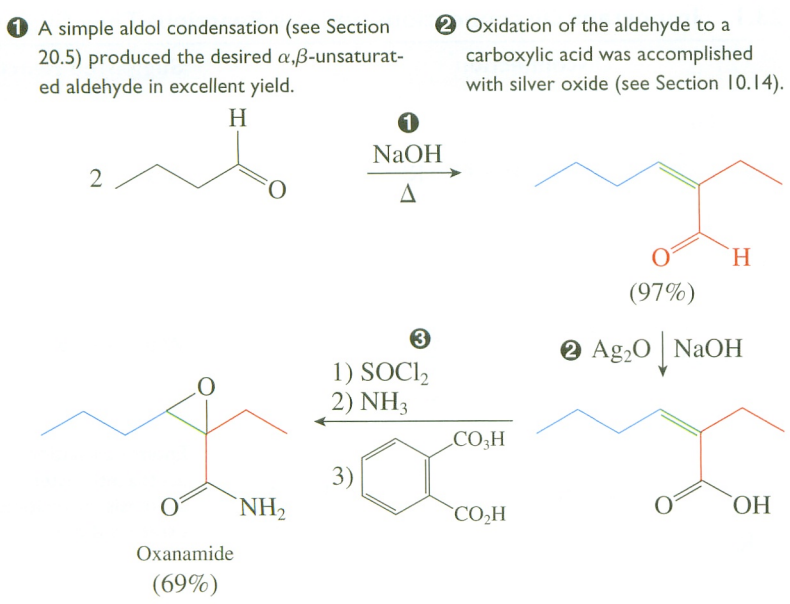


Figure 23.5

THE SYNTHESIS OF OXANAMIDE.

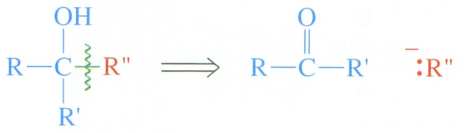
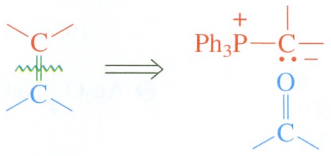
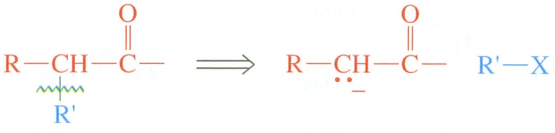
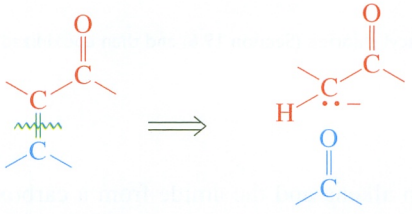
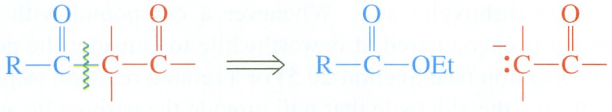
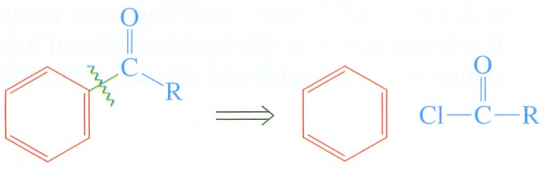
The epoxide can be prepared from an alkene and the amide from a carboxylic acid. The new target, 2-ethyl-2-hexenoic acid, has a CC double bond in conjugation with the carbonyl group of the carboxylic acid. Whenever a compound with an α,β-unsaturated carbonyl group is encountered, it is worthwhile to consider the possibility of using an aldol condensation (see Section 20.5) or a related reaction to prepare it. To examine this possibility, the aldehyde that will provide the carboxylic acid upon oxidation is disconnected at the double bond. Because both fragments produced by this disconnection are the same, it is apparent that an aldol condensation of butanal can be employed to prepare this compound. The synthesis was accomplished as shown in Figure 23.5.

23.7 Reactions That Form Carbon–Carbon Bonds

We have seen in this and previous chapters that carbon–carbon bond-forming reactions are of critical importance in designing a synthesis of an organic compound. As discussed in Section 23.6, it is often helpful to examine a synthetic target for certain structural features that suggest the use of a particular one of these reactions. Some of the more important disconnections that suggest specific carbon–carbon bond-forming reactions are listed in Table 23.1. (Remember, however, that there are many other ways to prepare these and other target compounds.)

Table 23.2 lists most of the carbon–carbon bond-forming reactions that have been presented in this text. It may prove helpful to consult this table when working synthesis problems. The more familiar you are with these reactions, the easier designing a synthesis will be.

Table 23.1 Important Disconnections and the Reactions They Suggest

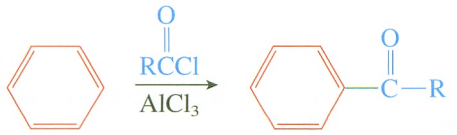
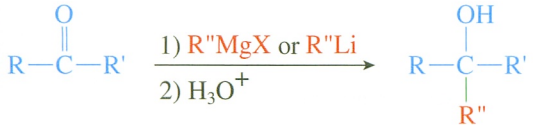
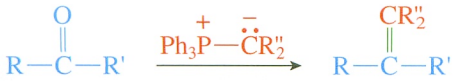
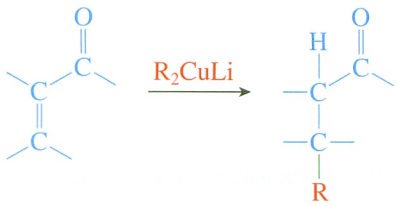
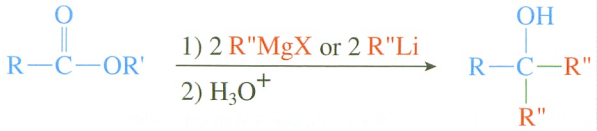
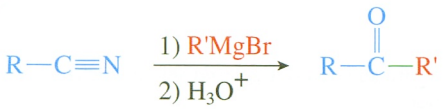
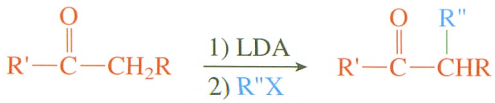
Disconnection	Suggested Reaction
	Grignard reaction
	Wittig reaction
	Enolate alkylation, acetoacetic ester synthesis, or malonic ester synthesis
	Aldol condensation
	Ester condensation
	Friedel-Crafts acylation
	Diels-Alder reaction

23.8 PREPARATION OF FUNCTIONAL GROUPS

Table 23.3 lists most of the reactions presented in preceding chapters that are useful in synthesis, including the reactions of Table 23.2. The reactions are grouped according to the functional group that is present in the product, rather than by their mechanisms. Thus, if an alcohol is the synthetic target, consultation of the appropriate section of the table will reveal a variety of methods that can be used to prepare alcohols.

Text continued on p. 1044.

Table 23.2 Some Important Carbon–Carbon Bond-Forming Reactions

Reaction	Section	Comments
$R{-}L + {}^{-}CN \longrightarrow R{-}CN$	10.8	S_N2, 1° and 2° R OK
$R{-}L + {}^{-}{:}C{\equiv}CR' \longrightarrow R{-}C{\equiv}CR'$	10.8	S_N2, 1° R only
	17.7	Friedel-Crafts alkylation, does not work for deactivated rings
	17.8	Friedel-Crafts acylation, does not work for strongly deactivated rings
	18.6	Grignard or organolithium addition
	18.7	Wittig reaction
	18.10	Conjugate addition of organocuprate reagents
	19.9	Grignard reagents or organolithium reagents plus esters give tertiary alcohols
	19.10	Acyl chlorides plus organocuprate reagents give ketones
	19.10	Nitriles plus Grignard reagents give ketones
	20.3	Alkylation of ketones, S_N2, R″ may be 1° (best) or 2°

Continued

Table 23.2 Some Important Carbon–Carbon Bond-Forming Reactions—cont'd

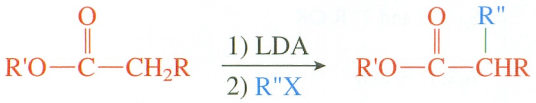
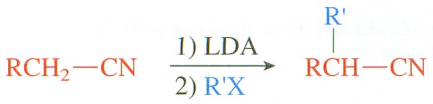
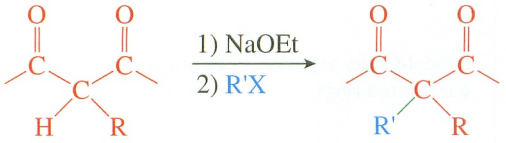
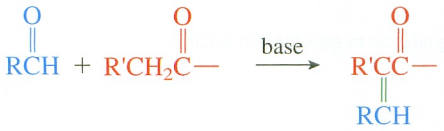
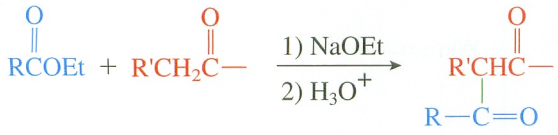
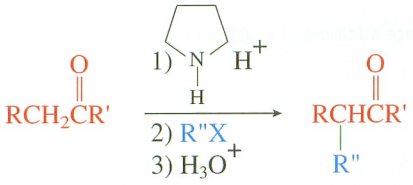
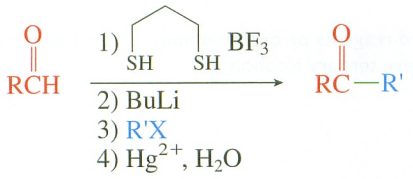
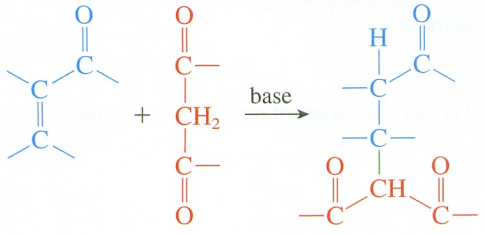
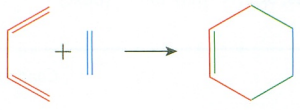
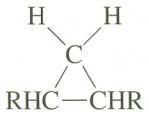
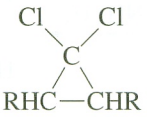
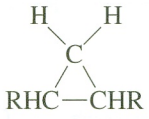
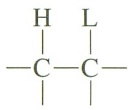
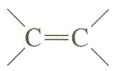
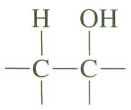
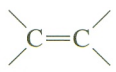
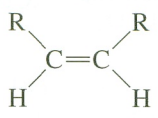
Reaction	Section	Comments
	20.3	Alkylation of esters, S_N2, R″ may be 1° (best) or 2°
	20.3	Alkylation of nitriles, S_N2, R′ may be 1° (best) or 2°
	20.4	Alkylation of stabilized anions, acetoacetic ester and malonic ester syntheses
	20.5	Aldol condensation
	20.6	Ester condensation
	20.8	Enamine reation, R″X must be very reactive
	20.9	Dithiane alkylation, acyl anion equivalent
	20.10	Conjugate addition of stabilized anions, Michael reaction
	22.6	Diels-Alder reaction

Table 23.3 Preparation of Functional Groups

	Reaction	Section	Comments
Alkanes	$R{-}L \xrightarrow[\text{or } NaBH_4]{LiAlH_4} R{-}H$	10.7	S_N2, 1° and 2° OK
	$RHC{=}CHR \xrightarrow[\Delta \text{ or } h\nu \text{ or } Cu^{2+}]{CH_2N_2}$ 	11.8	Syn addition
	$RHC{=}CHR \xrightarrow[NaOH]{CHCl_3}$ 	11.8	Syn addition
	$RHC{=}CHR \xrightarrow[Zn(Cu)]{CH_2I_2}$ 	11.8	Simmons-Smith reaction, syn addition
	$\begin{matrix}RHC{=}CHR \\ \text{or} \\ RC{\equiv}CR\end{matrix} \xrightarrow[Ni, Pd, \text{ or } Pt]{H_2} RCH_2CH_2R$	11.12	Syn addition
	$R{-}\overset{\overset{O}{\|}}{C}{-}R' \xrightarrow[\text{or}\\ NH_2NH_2\\ KOH, \Delta]{Zn(Hg), HCl} R{-}CH_2{-}R'$	17.13	Clemmensen reduction (H_2/Pd can be used when R = Ar)
		18.8	Wolff-Kishner reduction
	$RBr \xrightarrow[[AIBN]]{Bu_3SnH} RH$	21.7	Radical chain mechanism
Alkenes	 $\xrightarrow[\text{or } {}^-OR]{{}^-OH}$ 	10.11	E2, Zaitsev's rule, usually anti elimination
	 $\xrightarrow[\text{or}\\ H_3PO_4\\ \Delta]{H_2SO_4}$ 	10.13	Usually E1, Zaitsev's rule
	$R{-}C{\equiv}C{-}R \xrightarrow[\text{Lindlar catalyst}]{1\ H_2}$ 	11.12	Syn addition

Continued

Table 23.3 Preparation of Functional Groups—cont'd

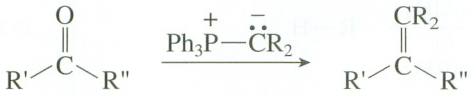
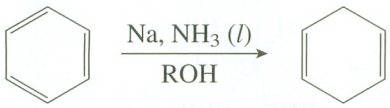
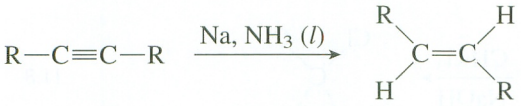
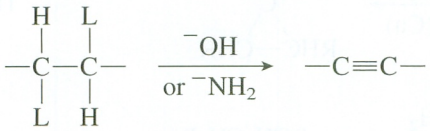
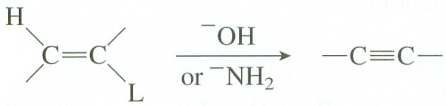
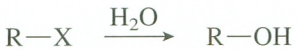
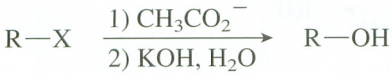
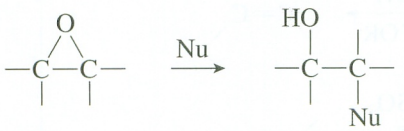
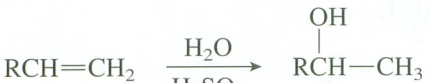
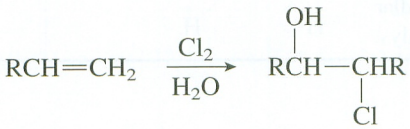
	Reaction	Section	Comments
Alkenes —cont'd		18.7	Wittig reaction
		21.10	Birch reduction
		21.10	Anti addition
Alkynes		10.8	S_N2, 1° R only
		10.12	E2
		10.12	E2
Alcohols		10.2	S_N2, best with 1° R
		10.2	S_N1, OK with 2° and 3° R
		10.2	S_N2, good with 1° and 2° R, synthetic equivalent of hydroxide ion
		10.10	Epoxide opening
		11.3	Hydration, low yields, rearrangements may occur, Markovnikov's rule
		11.5	Halohydrin formation, anti addition, OH on more substituted carbon

Table 23.3 Preparation of Functional Groups—cont'd

	Reaction	Section	Comments
Alcohols—cont'd	$RCH{=}CH_2 \xrightarrow[2)\ NaBH_4,\ NaOH]{1)\ Hg(O_2CCH_3)_2,\ H_2O} RCH(OH){-}CH_3$	11.6	Oxymercuration–reduction, no rearrangements, Markovnikov's rule
	$RCH{=}CH_2 \xrightarrow[2)\ H_2O_2,\ NaOH]{1)\ BH_3,\ THF} RCH(OH){-}CH_2$	11.7	Hydroboration–oxidation, syn addition, anti-Markovnikov
	$RCH{=}CHR \xrightarrow[KMnO_4,\ NaOH]{OsO_4\ \text{or}} RCH(OH){-}CHR$	11.10	Syn addition
	$R{-}C(=O){-}R' \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4\ \text{or}\ NaBH_4} R{-}C(OH)(H){-}R'$	18.2	Reduction of aldehydes and ketones
	$R{-}C(=O){-}R' \xrightarrow[2)\ H_3O^+]{1)\ R''MgX\ \text{or}\ R''Li} R{-}C(OH)(R''){-}R'$	18.6	Addition of Grignard and organolithium reagents to aldehydes and ketones
	$R{-}C(=O){-}OR'\ \text{or}\ R{-}C(=O){-}OH \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} R{-}C(OH)(H){-}H$	19.7	Reduction of carboxylic acids and esters, $LiAlH_4$ required
	$R{-}C(=O){-}OR' \xrightarrow[2)\ H_3O^+]{1)\ 2\ R''MgX\ \text{or}\ 2\ R''Li} R{-}C(OH)(R''){-}R''$	19.9	Addition of Grignard and organolithium reagents to esters, adds two identical R″ groups
Ethers	$R{-}L \xrightarrow{{}^-OR'} R{-}OR'$	10.3	Williamson ether synthesis, S_N2, best with 1° R
	$R{-}L \xrightarrow{HOR'} R{-}OR'$	10.3	S_N1, OK with 2° and 3° R

Continued

Table 23.3 Preparation of Functional Groups—cont'd

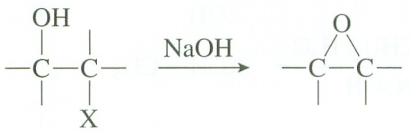
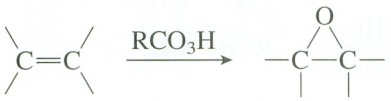
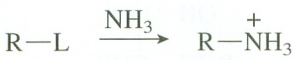
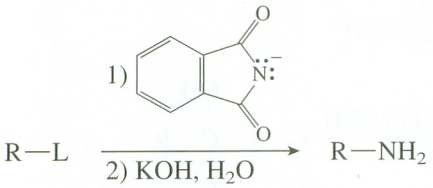
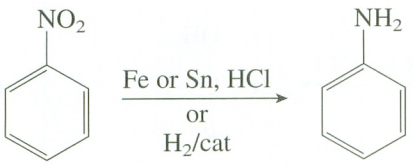
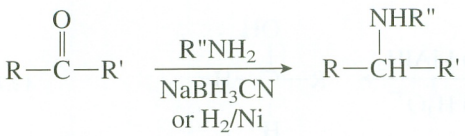
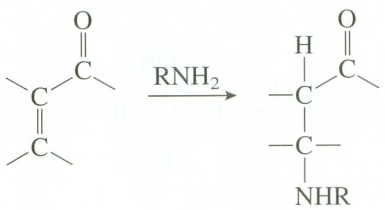
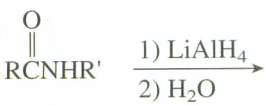
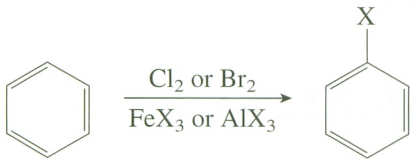
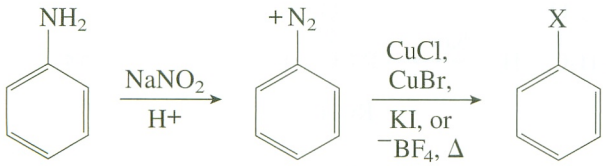
	Reaction	Section	Comments
Epoxides		11.5	Intramolecular S_N2
		11.9	Syn addition
Amines		10.6	S_N2, multiple alkylation problems
		10.6	Gabriel synthesis, S_N2, 1° and 2° R OK
		17.13	Reduction of aromatic nitro compounds
		18.8	Reductive amination
		18.10	Conjugate addition
		19.7	Reduction of amides
		19.7	Reduction of nitriles

Table 23.3 Preparation of Functional Groups—cont'd

	Reaction	Section	Comments
Halides	$R{-}OH \xrightarrow{HX} R{-}X$	10.5	Chlorides require $ZnCl_2$ for 1° and 2° R
	$R{-}OTs \xrightarrow{X^-} R{-}X$	10.5	S_N2 conditions
	$R{-}OH \xrightarrow{SOCl_2} R{-}Cl$	10.5	Thionyl chloride
	$R{-}OH \xrightarrow{PBr_3} R{-}Br$	10.5	Phosphorus tribromide
	$R{-}OH \xrightarrow{PI_3} R{-}I$	10.5	Phosphorus triiodide
	$R{-}CH{=}CH_2 \xrightarrow{HX} R{-}\underset{\displaystyle X}{\overset{\displaystyle H}{CH}}{-}CH_2$	11.2	Markovnikov's rule
	$RCH{=}CHR' \xrightarrow[\text{or } Br_2]{Cl_2} RCH(X){-}CHR'(X)$	11.4	Anti addition
	$RCH{=}CHR' \xrightarrow[H_2O]{X_2} RCH(X){-}CHR'(OH)$	11.5	Halohydrin formation, anti addition, Markovnikov's rule
		17.5	Electrophilic aromatic substitution
		17.10	Substitutions via diazonium ion
	$RCCH_3 \xrightarrow[HX]{X_2} RCCH_2X$	20.2	Bromination or chlorination

Continued

Table 23.3 Preparation of Functional Groups—cont'd

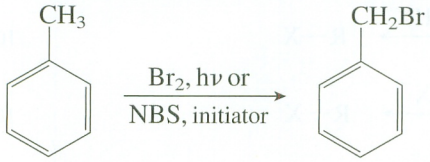
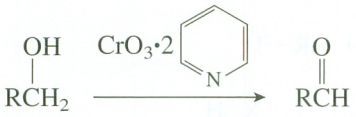
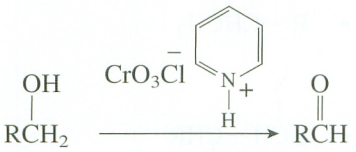
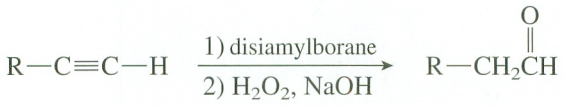
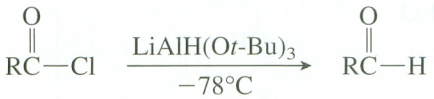
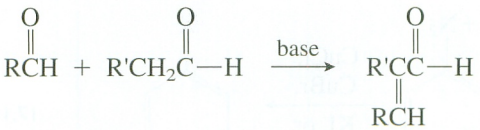
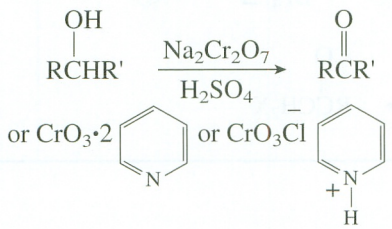
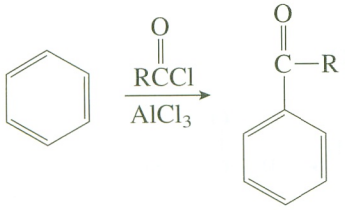
	Reaction	Section	Comments
Halides—cont'd		21.6	Used for allylic bromides also, radical chain mechanism
		21.9	Anti-Markovnikov regiochemistry, HBr only, radical chain mechanism
Aldehydes		10.14	Oxidation using chromium trioxide–pyridine complex
		10.14	Oxidation using pyridinium chlorochromate (PCC)
		11.7	Hydroboration of terminal alkynes
		19.8	Selective reduction of acyl chlorides
		19.8	Selective reduction of esters with diisobutylaluminum hydride
		20.5	Aldol condensation
Ketones		10.14	Oxidation

Table 23.3 Preparation of Functional Groups—cont'd

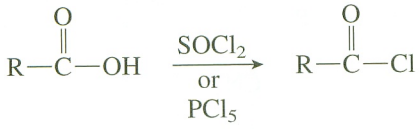
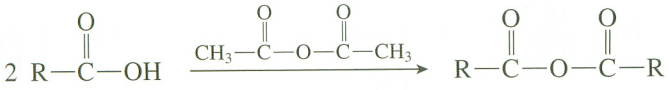
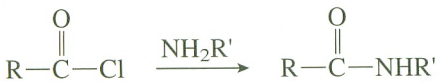
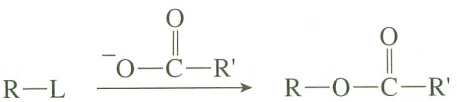
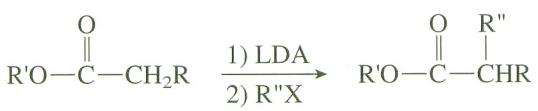
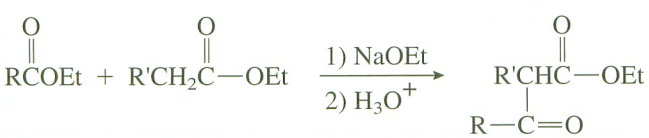
	Reaction	Section	Comments
Ketones—cont'd	$R-C\equiv C-H \xrightarrow[H_2SO_4,\ HgSO_4]{H_2O} RCCH_3$	11.6	Hydration of alkynes, Markovnikov regiochemistry, alkyne should be terminal or symmetrical
	$R-C\equiv C-R \xrightarrow[2)\ H_2O_2,\ NaOH]{1)\ BH_3,\ THF} RCCH_2R$	11.7	Hydroboration of alkynes, alkyne should be symmetrical
		17.8	Friedel-Crafts acylation, does not work when ring has strong deactivating substituents
	$R-CCl \xrightarrow{R'_2CuLi} R-CR'$	19.10	Addition of organocuprate reagents to acyl chlorides
	$R-C\equiv N \xrightarrow[2)\ H_3O^+]{1)\ R'MgBr} R-CR'$	19.10	Addition of Grignard reagents to nitriles
	$R'-CCH_2R \xrightarrow[2)\ R''X]{1)\ LDA} R'-CCHR$	20.3	Alkylation of ketones, S_N2, R" may be 1° (best) or 2°, regiochemistry must be controlled somehow
	$H_3C-CCH_2COEt \xrightarrow[2)\ RL\ 3)\ KOH,\ H_2O\ 4)\ H_3O^+,\ \Delta]{1)\ NaOEt} H_3C-CCH_2R$	20.4	Acetoacetic ester synthesis, S_N2, R must be 1° or 2°
	$RCH + R'CH_2C-R'' \xrightarrow[\Delta]{base} R'CC-R''$ (RCH)	20.5	Aldol condensation

Continued

Table 23.3 Preparation of Functional Groups—cont'd

	Reaction	Section	Comments
Ketones—cont'd	$RCH_2CR' \xrightarrow[2)\ R''X \\ 3)\ H_3O^+]{1)\ \text{pyrrolidine, HA}} RCHCR'$ (R'')	20.8	Enamine reaction, R"X must be very reactive
	$RCH \xrightarrow[2)\ BuLi \\ 3)\ R'X \\ 4)\ Hg^{2+},\ H_2O]{1)\ \text{dithiane, } BF_3} RC{-}R'$	20.9	Dithiane alkylation, acyl anion equivalent, S_N2, R' must be 1° or 2°
Carboxylic Acids	$R{-}C{-}H \xrightarrow[\text{or}\ KMnO_4]{Ag_2O,\ NaOH} R{-}C{-}OH$	10.14	Oxidation of aldehydes
	$\xrightarrow[2)\ H_3O^+]{1)\ KMnO_4,\ NaOH}$	17.13	Any alkyl group, except tertiary ones, can be oxidized to the benzoic acid derivative
	$RMgX \text{ or } RLi \xrightarrow[2)\ H_3O^+]{1)\ CO_2} R{-}CO_2H$	18.6	Reaction of Grignard reagents with carbon dioxide
	$R{-}C{-}L \xrightarrow[H_3O^+ \text{ or } {}^-OH]{H_2O} R{-}C{-}OH$	19.5	Any carboxylic acid derivative can be hydrolyzed to a carboxylic acid
	$R{-}C{\equiv}N \xrightarrow[H_3O^+ \text{ or } {}^-OH]{H_2O} R{-}C{-}OH$	19.5	Nitriles can also be hydrolyzed to carboxylic acids
	$EtO{-}C(=O){-}CH_2{-}C(=O){-}OEt \xrightarrow[2)\ RL \\ 3)\ KOH,\ H_2O \\ 4)\ H_3O^+,\ \Delta]{1)\ NaOEt} HO{-}C(=O){-}CH_2R$	20.4	Malonic ester synthesis, S_N2, R must be 1° or 2°

Table 23.3 Preparation of Functional Groups—cont'd

	Reaction	Section	Comments
Acyl Chlorides		19.2	
Anhydrides		19.3	Only symmetrical anhydrides are usually prepared
		19.3	Anhydride exchange
Amides		19.6	
		19.6	
Esters		10.4	S_N2, OK for 1° and 2°
		19.4	
		19.4	
		19.4	Fischer esterification
		20.3	S_N2, R″ may be 1° (best) or 2°
		20.6	Ester condensation

Continued

Table 23.3 Preparation of Functional Groups—cont'd

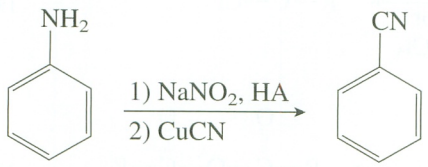
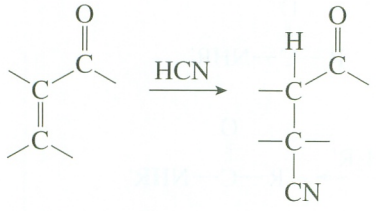
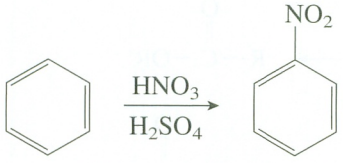
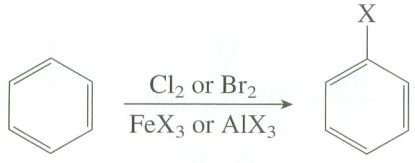
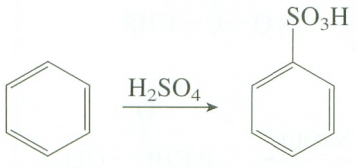
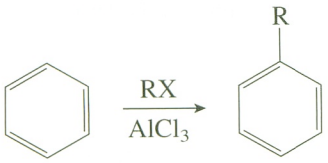
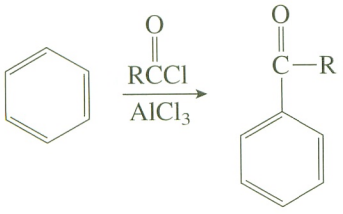
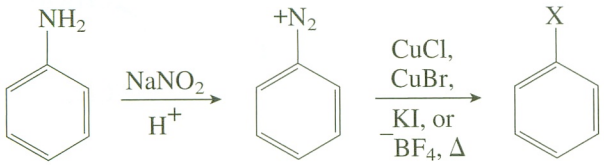
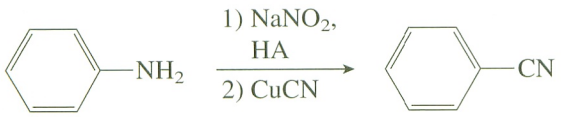
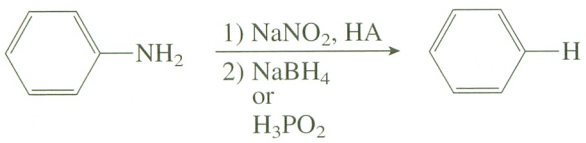
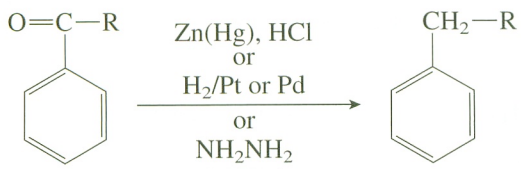
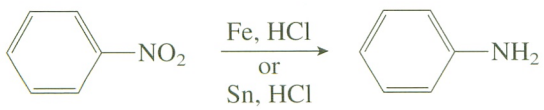
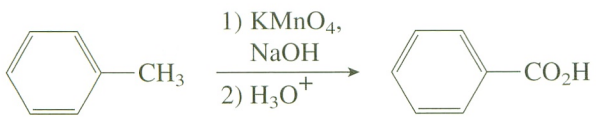
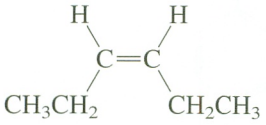
	Reaction	Section	Comments
Nitriles	$R{-}L + {}^{-}CN \longrightarrow R{-}CN$	10.8	S_N2, OK with 1° and 2°
		17.10	Via diazonium ion
		18.4	Cyanohydrin formation
		18.10	Conjugate addition
	$RCH_2{-}CN \xrightarrow[2)\ R'X]{1)\ LDA} RCH(R')-CN$	20.3	S_N2, R′ may be 1° (best) or 2°
Aromatic Compounds		17.4	Electrophilic aromatic substitution
		17.5	Electrophilic aromatic substitution
		17.6	Electrophilic aromatic substitution, reversible in H_2O/H_2SO_4

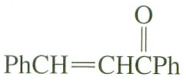
Table 23.3 Preparation of Functional Groups—cont'd

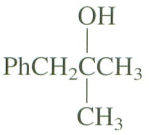
	Reaction	Section	Comments
Aromatic Compounds		17.7	Friedel-Crafts alkylation, rearrangements, multiple alkylation, fails with deactivated rings
		17.8	Friedel-Crafts acylation, fails with strongly deactivated rings
		17.10	Via diazonium ion
		17.10	Via diazonium ion
		17.10	Via diazonium ion
		17.13 18.8	Clemmensen reduction or hydrogenolysis, or Wolff-Kishner reduction
		17.13	Reduction of nitro groups
		17.13	Oxidation of any alkyl group except tertiary

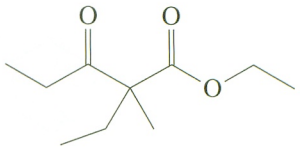
PROBLEM 23.11

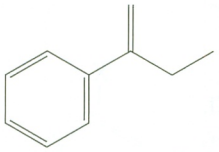
Suggest syntheses of these compounds. Each synthesis should involve the formation of at least two carbon–carbon bonds. Make sure that your synthesis produces the correct stereochemistry where it is shown in the target compound.

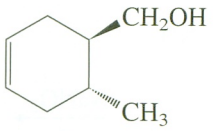
a) 

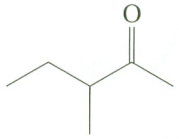
b) 

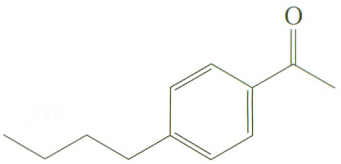
c) 

d) 

e) 

f) 

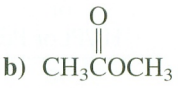
g) 

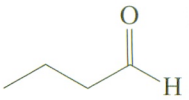
h) 

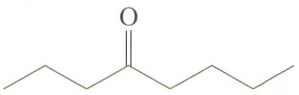
PROBLEM 23.12

Show syntheses of these compounds using methanol, ethanol, and benzene as the only sources for the carbons in the compounds. You may use any solvents or inorganic reagents that you need. Once you have made a compound, you may use it in the synthesis of any subsequent compound.

a)

b) 

c) 

d) 

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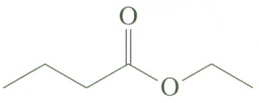
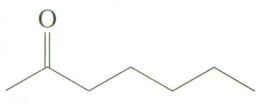
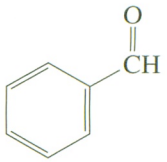
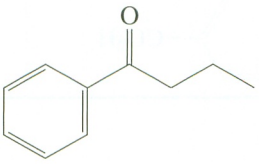
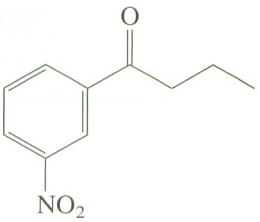
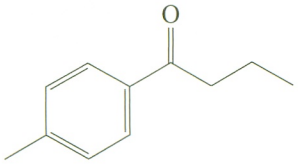
f) 

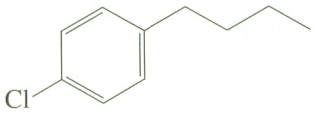
g) 

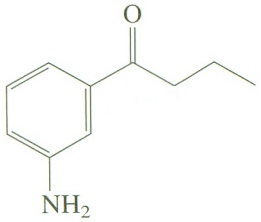
h) 

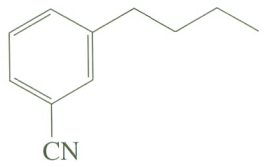
i) 

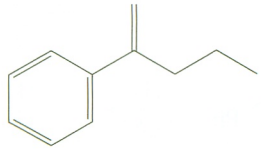
j) 

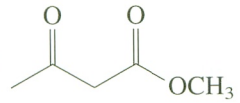
k) 

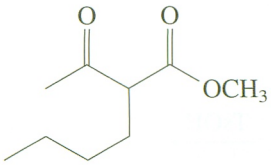
l) 

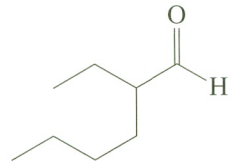
m) 

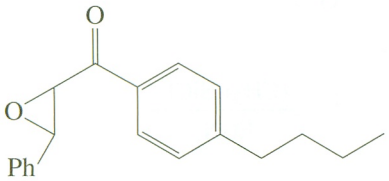
n) 

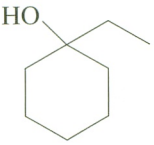
o) 

p) 

q) 

r) 

s) 

t) 

Review of Mastery Goals

After completing this chapter, you should be able to:

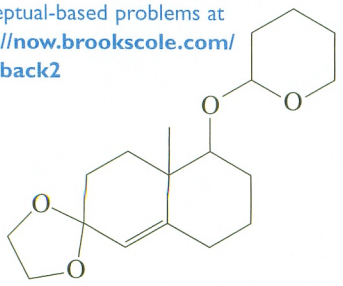
- Recognize when a protecting group is needed and how to use it in the synthesis of an organic compound. (Problem 23.17)
- Use retrosynthetic analysis to design syntheses of more complex organic compounds. (Problems 23.14, 23.15, 23.16, 23.18, and 23.19)

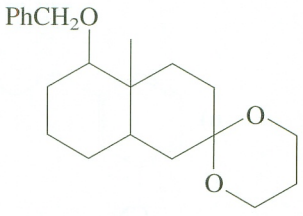
ORGANIC Chemistry Now™
Click *Mastery Goal Quiz* to test how well you have met these goals.

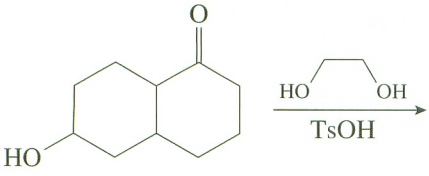
ORGANIC Chemistry Now™
Assess your understanding of this chapter's topics with additional quizzing and conceptual-based problems at **http://now.brookscole.com/hornback2**

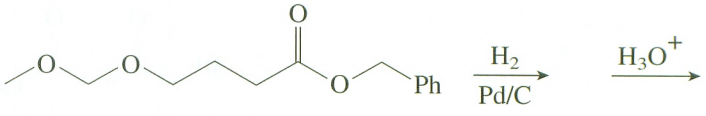
Additional Problems

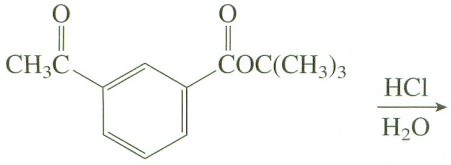
23.13 Show the products of these reactions:

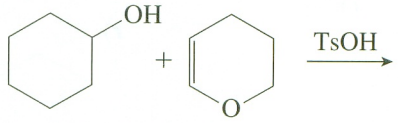
a) 

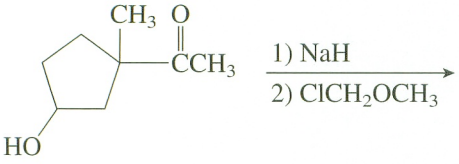
b) 

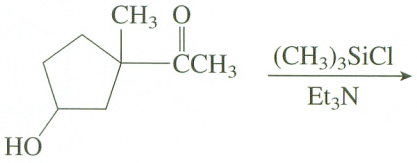
c) 

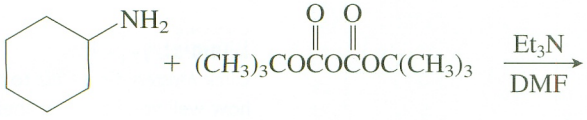
d) 

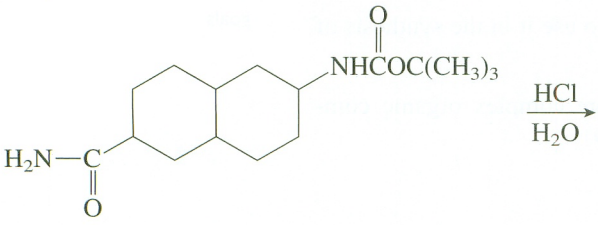
e) 

f) 

g) 

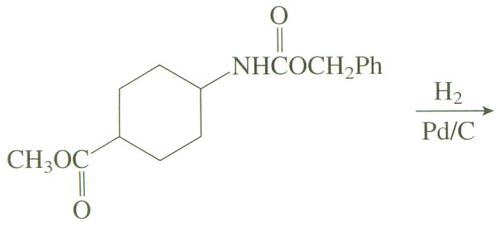
h) 

i) 

j) 

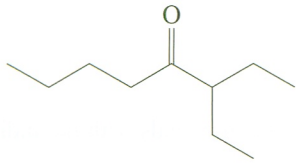
k)

l)

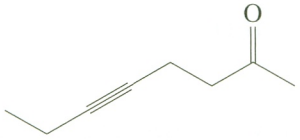


23.14 Use disconnections of carbon–carbon bonds to generate electrophile and nucleophile synthon fragments that could be used to prepare these compounds. Then show an actual reaction suggested by these synthons that would provide a method for the synthesis of each compound. Design at least three different routes to each compound.

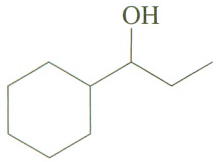
a)



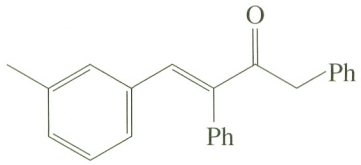
b)



c)

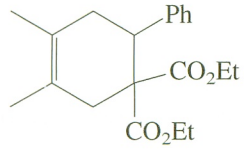


d)



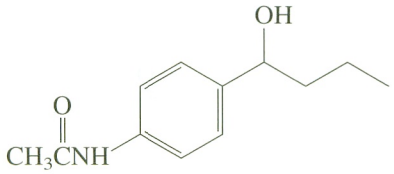
23.15 Show syntheses of these compounds from compounds with the indicated number of carbons:

a)



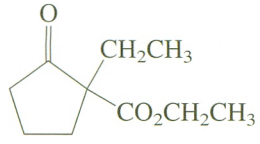
(7 carbons or fewer)

b)



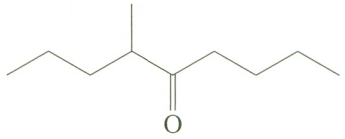
(6 carbons or fewer)

c)



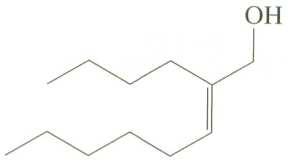
(6 carbons or fewer, no rings)

d)



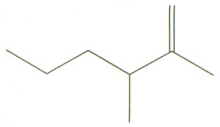
(5 carbons or fewer)

e)



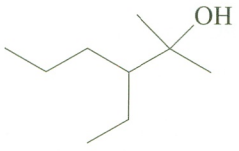
(6 carbons or fewer)

f)



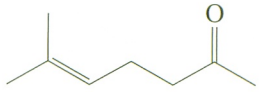
(4 carbons or fewer)

g)



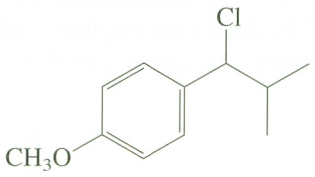
(4 carbons or fewer)

h)



(5 carbons or fewer)

i)

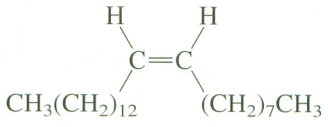


(benzene)

BioLink

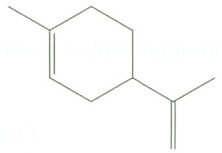
23.16 Show syntheses of these compounds from compounds with the indicated number of carbons:

a)



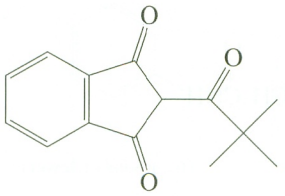
Muscalure (sex pheromone of the female housefly)
(from compounds with 13 carbons or fewer)

b)



Limonene (constituent of lemon peel)
(from compounds with 5 carbons or fewer)

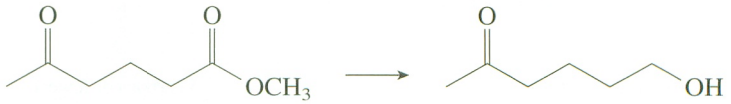
c)

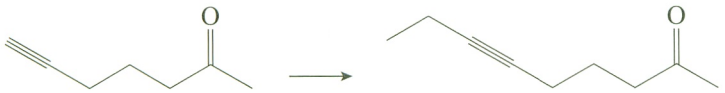


Pival (a rat poison)
(from compounds with 9 carbons or fewer)

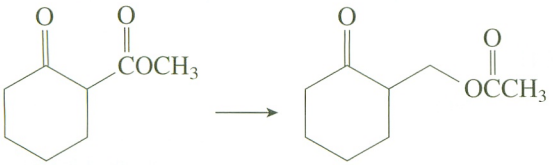
23.17 Show a series of reactions that will accomplish these transformations. The use of protecting groups is necessary.

a)

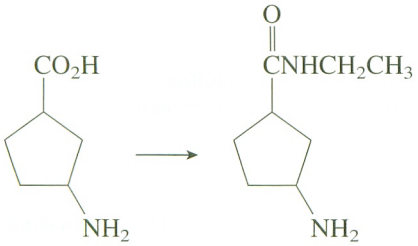


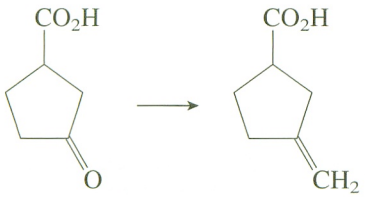
b) 

c)

d) 

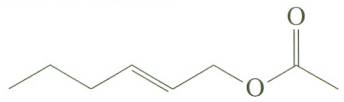
e) $HOCH_2C{\equiv}CH \longrightarrow HOCH_2C{\equiv}C{-}CO_2H$

f) 

g) 

23.18 Show syntheses of these compounds from compounds with the indicated number of carbons:

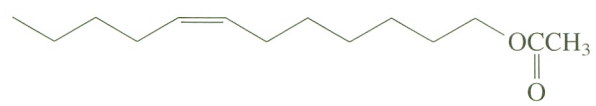
BioLink

a) 

Sex pheromone of Indian water bug
(from compounds with 3 carbons or fewer)
(ignore stereochemistry)

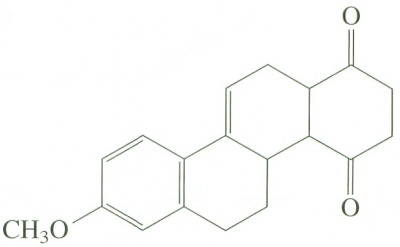
b) $CH_3(CH_2)_3CH{=}CHCH_2CH_2CH{=}CH(CH_2)_6OCCH_3$ (O above the carbonyl carbon)

Gossyplure (sex pheromone of pink bollworm moth, a severe cotton pest)
(from compounds with 8 carbons or fewer)

c) 

(Z)-7-Dodecen-1-yl acetate (sex attractant of elephants and moths)
(from compounds with 6 carbons or fewer)

d)

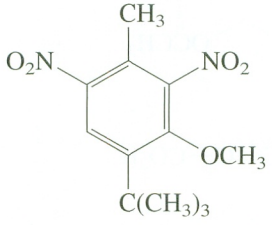


(Used in the synthesis of estrone, a human sex hormone) (from compounds with 11 carbons or fewer)

BioLink

23.19 Show syntheses of these compounds from compounds with the indicated number of carbons:

a)

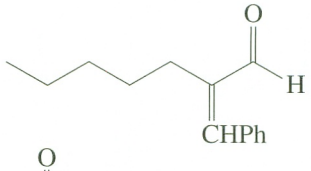


Musk ambrette, a perfume ingredient (from compounds with 7 carbons or fewer)

b) $PhCH_2OCPh$

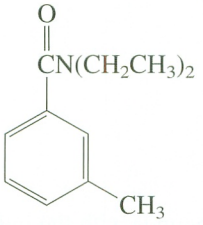
Perfume ingredient and insect repellent (from compounds with 6 carbons or fewer)

c)



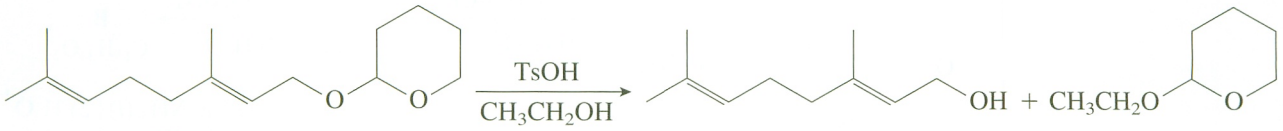
Flosal, a perfume ingredient (from compounds with 6 carbons or fewer)

d)



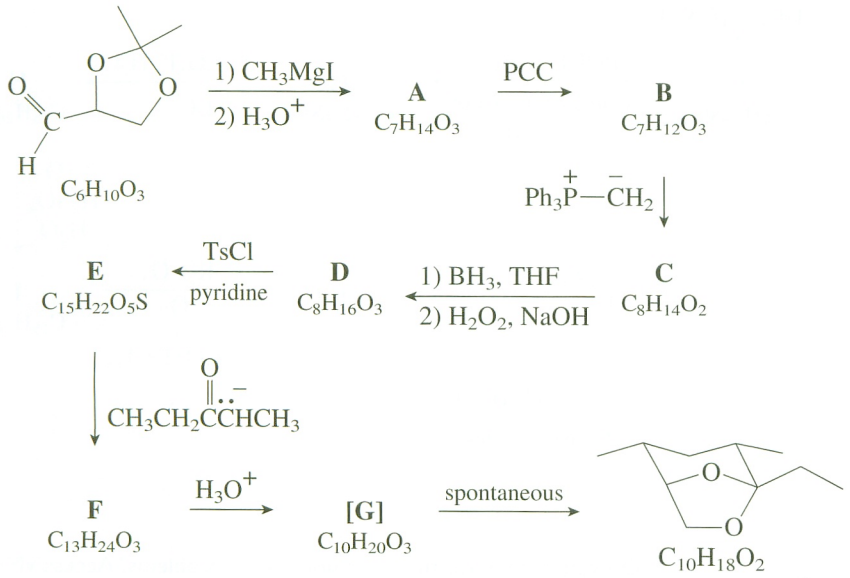
N,N-Diethyl-*m*-toluamide, an insect repellent (from compounds with 7 carbons or fewer)

23.20 Show the steps in the mechanism for the hydrolysis of this tetrahydropyranyl ether:



23.21 Show the missing structures in this reaction sequence. This type of problem is sometimes called a road-map problem. Keep both the initial and final structure in mind and don't forget to use the information in the formulas of the missing compounds.

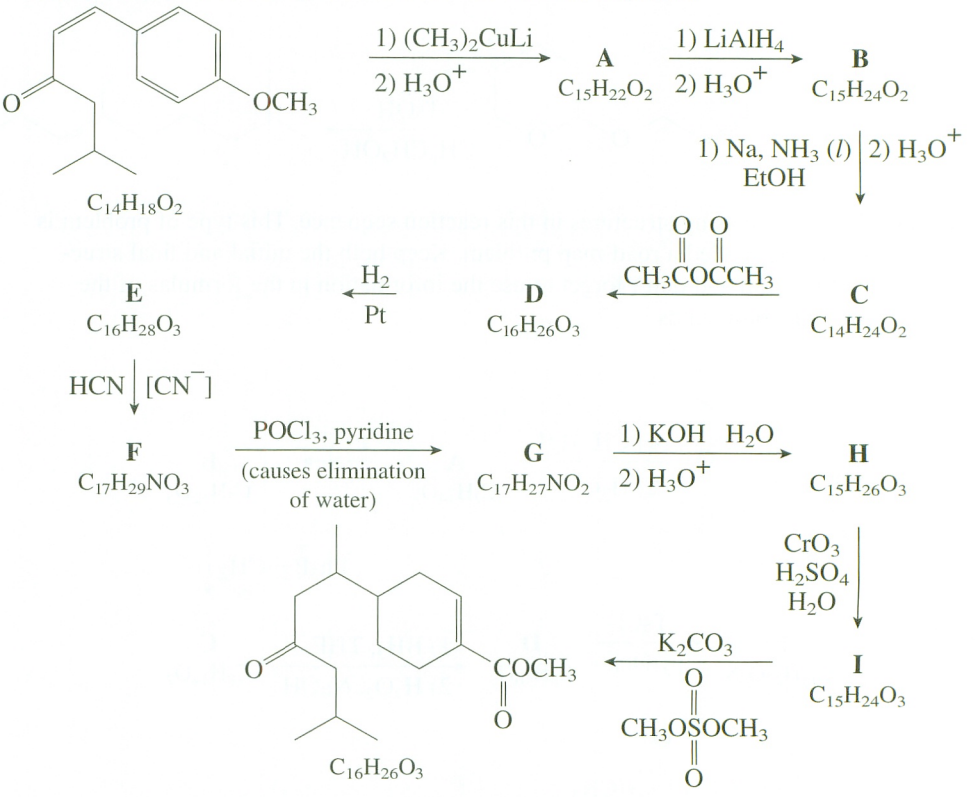
BioLink



α-Multistriatin, an insect pheromone

BioLink

23.22 Show the missing structures in this reaction sequence:



Juvabione, an insect hormone mimic

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